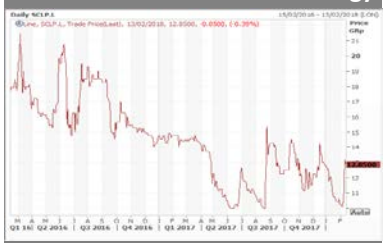
hardman&co

Pharmaceuticals & Biotechnology



Source: Eikon Thomson Reuters

Market data	
EPIC/TKR	**SCLP**
Price (p)	12.5
12m High (p)	17.0
12m Low (p)	9.7
Shares (m)	312.1
Mkt Cap (£m)	39.0
EV (£m)	34.0
Free Float*	78%
Market	AIM

**As defined by AIM Rule 26*

Description

Scancell is a clinical-stage company focused on the discovery and development of two proprietary immunotherapy platforms, Moditope and ImmunoBody, with the potential to be used as therapeutic cancer vaccines.

Company information	
Exec Chairman	John Chiplin
CEO	Cliff Holloway
CSO	Prof. Lindy Durrant
US Office	+1 858 900 2646
UK HQ	+44 1865 338 069
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Key shareholders	
Directors	6.0%
Calculus Capital	16.1%
Legal & General	5.1%
Hygea VCT	4.2%
Oxford Technology	3.6%

Diary	
2Q'18	US IND SCIB1 + CPI
4Q'18	SCIB1 Phase II
Sep'18	Finals

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Scancell Holdings

Validating and de-risking of multiple opportunities

Scancell is a clinical-stage biotechnology company developing two distinct flexible cancer immunotherapy platforms, each with broad applications: ImmunoBody is a DNA vaccine that stimulates high-avidity anti-tumour $CD8^+$ T-cells for use as a monotherapy or in combination with checkpoint inhibitors (CPIs); Moditope targets modified antigens and stimulates powerful anti-tumour $CD4^+$ T-cell responses for use in advanced and hard-to-treat cancers. Both technologies have been externally validated recently through partnership deals with Cancer Research UK (CRUK; ImmunoBody SCIB2) and BioNTech (Moditope), providing significant endorsements.

- **Strategy**: Scancell is developing two proprietary immuno-oncology platforms that target cancer cells directly to produce potent T-cell responses. Both technologies are highly flexible, potentially targeting many types of cancer. The initial aim is to complete proof-of-concept trials in multiple indications.

- **ImmunoBody:** After exceptional five-year survival data in a proof-of-concept trial in late-stage melanoma patients and evidence of tumour rejection, Scancell will advance both SCIB1 (melanoma) and SCIB2 (with CRUK in lung cancer) in combination trials with a CPI. Headline data should start to emerge from 1H'19.

- **Moditope:** This technology exploits the normal immune response to stressed cells in order to eradicate cancer cells through immunisation. The clinical lead, Modi-1, is expected to enter a Phase I/II proof-of-concept trial, initially in triple negative breast cancer, ovarian cancer and sarcoma in 1H calendar 2019.

- **Risks:** Scancell is an early-stage drug development company carrying a high risk that a product may fail in clinical trials. Its focus on cancer immunotherapy is extremely exciting, but it is a competitive field. The novelty of its technologies has been endorsed through recent partnerships with CRUK and BioNTech.

- **Investment summary:** Scancell is trading on an EV of ca.£34m, compared with a cumulative investment of £29m to get the company to where it is today, which is low compared to its relevant peers. Scancell's proprietary technologies are in the 'hot' area of immuno-oncology and targeting markets of significant unmet medical need. Recent deals have demonstrated the price that big pharma is willing to pay for validated assets in the field.

Financial summary and valuation

Year-end April (£m)	2015	2016	2017	2018E	2019E	2020E
Sales	0.00	0.00	0.00	0.0	0.0	0.0
R&D investment	-2.12	-2.01	-2.77	-3.5	-5.9	-7.6
SG&A	-0.75	-1.00	-1.73	-2.0	-2.1	-2.2
Underlying EBIT	-2.87	-3.01	-4.50	-5.5	-8.0	-9.8
Reported EBIT	-2.96	-3.04	-4.55	-5.6	-8.1	-9.9
Underlying PBT	-2.74	-2.99	-4.44	-5.5	-7.9	-9.8
Statutory PBT	-2.83	-3.03	-4.50	-5.5	-8.0	-9.9
Underlying EPS (p)	-1.03	-1.12	-1.34	-1.5	-1.7	-2.1
Statutory EPS (p)	-1.07	-1.14	-1.36	-1.5	-1.7	-2.1
Net (debt)/cash	3.06	6.53	2.67	12.3	5.1	-3.5
Capital increase	0.00	5.79	0.00	14.1	0.0	0.0
P/E (x)	-	-	-	-	-	-

Source: Hardman & Co Life Sciences Research

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Executive summary

Background

Scancell Holdings is a clinical-stage biotechnology company that is developing in parallel two distinct cancer immunotherapy platforms – ImmunoBody and Moditope – which employ different approaches to trigger cancer-specific immune responses. Strong science is at the heart of Scancell, as evidenced by its co-founder leading a high-profile team shortlisted for CRUK's prestigious Grand Challenge award, and by worldwide recognition through recent collaborations.

In May 2017, Scancell raised £5m (gross) to prepare the groundwork for taking both platforms to the next stage of clinical development. This has resulted in the advancement and expansion of internal projects. In addition, both platforms have recently received external validation through the announcements of collaboration deals with CRUK (ImmunoBody) and BioNTech (Moditope).

Moditope

MODITOPE®

Modi-1 & Modi-2

- Innovative mechanism of action potentially targets all solid tumours
- Broad patent filing offers potential to dominate the use of citrullinated peptides for the treatment of cancer
- Modi-1 and Modi-2 will target tumours that are unresponsive to checkpoint inhibitor therapy (turning "cold" tumours to "hot")
- Identification of Modi-specific TCRs provides a novel pathway for CD4-based TCR therapy

Source: Scancell

Moditope

Moditope is the first vaccine type to target amino acid modifications produced by enzymes induced by cellular stress to elicit an immune response. By their very nature, cancer cells are rapidly dividing and therefore require a plentiful supply of nutrients to proliferate and survive, creating a 'stressed' environment. Scancell is the first company in the world to demonstrate that tumour cells, in which these modified neo-epitopes are expressed, are excellent targets for vaccine therapy.

- Modified citrullinated peptides that induce potent killer $CD4^+$ T-cells that target neo-epitopes.
- Clinical lead, Modi-1, being prepared for clinical trials, initially in triple negative breast cancer, ovarian cancer and sarcoma, which are expected to start in 1H calendar 2019.
- Pre-clinical programme underway for Modi-2, targeting multiple solid tumours. Pre-clinical development of selected epitopes is planned for 2018.
- Research collaboration with leading European immuno-oncology company BioNTech for the research and development of T-cell receptor (TCR) therapies based on Mod-1 citrullinated peptides.

ImmunoBody

IMMUNOBODY®

SCIB1

- In combination with checkpoint inhibitors in patients with late stage disease to increase efficacy without compromising safety
- As monotherapy in patients with resected disease (adjuvant setting) to delay or prevent recurrence

SCIB2

- Lung cancer represents a huge unmet medical need; deaths per year greater than melanoma, colon, breast and prostate cancers combined
- Checkpoint inhibitors less effective in lung cancer, with 80% of patients requiring a better standard of care

Source: Scancell

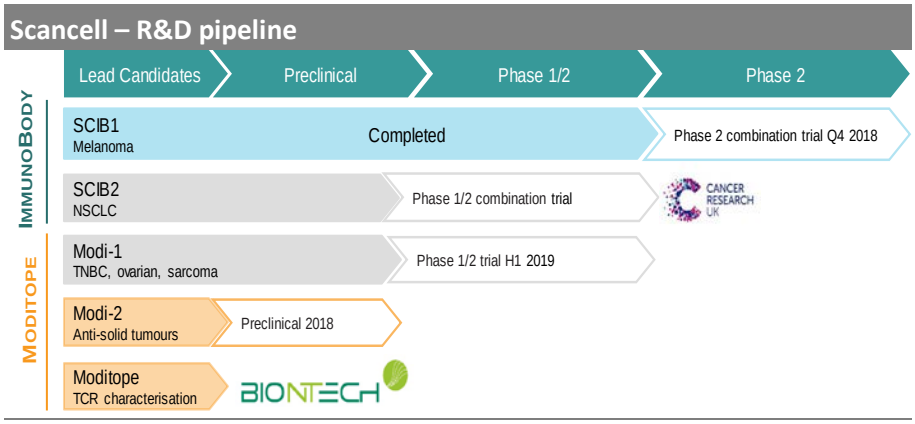
ImmunoBody

ImmunoBody is an innovative DNA-based immunotherapy platform that generates high-avidity $CD8^+$ T-cell responses through a dual mode of action – direct- and cross-presentation – which can kill tumour cells. In contrast, traditional vaccine immunisation frequently induces only low-avidity T-cell responses which are not strong enough to kill tumour cells.

- Dual mechanism of action produces a synergistic 100-fold enhancement in T-cell avidity vital for tumour cell death.
- Unprecedented five-year clinical outcomes with SCIB1 in patients with resected late-stage malignant melanoma.
- Phase I/II SCIB2 trial in lung cancer patients to be funded and managed by CRUK.

Development pipeline

Scancell's R&D pipeline is comprised of four lead products, two from each platform, initially targeting five cancers with unmet needs. In addition, it has recently announced a research collaboration with Europe's premier immuno-oncology company, BioNTech, for research into TCR therapies.



Source: Scancell

On the back of unprecedented five-year survival data from a proof-of-concept trial of SCIB1 in patients with resected late-stage melanoma combined with tumour regression in non-resected patients, Scancell has planned a follow-up Phase II trial in combination with a CPI; although the use of CPIs has improved the prognosis for many melanoma patients, a significant proportion of patients do not respond to these new regimes. In addition, a Phase I/II trial with SCIB2 is going to be managed and funded by its recently announced partner, CRUK. Following the trial, Scancell has the pre-agreed option to acquire the data. This deal is good for four reasons: i) it represents an external validation of the ImmunoBody technology; ii) it has freed up Scancell's resources to advance its other clinical programmes; iii) Scancell can re-acquire the product and data for a reasonable sum; iv) if Scancell does not elect to re-acquire the product then the parties will enter into a revenue share agreement if CRUK decides to commercialise the product independently.

Modi-1, the company's first product from the Moditope platform is on the verge of Good Manufacturing Practice (GMP) manufacturing in advance of initiating a Phase I/II trial in triple negative breast cancer, ovarian cancer and sarcoma. The programme has benefited from the identification of an adjuvant which, when covalently linked to the Moditope peptides, reduces the effective dose significantly, providing improved scaling of the dose for human studies. Components of the next product, Modi-2, have been identified in readiness for pre-clinical characterisation during the next 12 months.

Commercial opportunity

Although Scancell is operating in a very competitive environment, and despite all the research and commercialisation of new drugs, there is still a desperate need for new, effective cancer drugs. The fact that Scancell has two novel and distinct proprietary platforms demonstrates that the company is well positioned in this complex field.

Because cancer is frequently treated with a cocktail of drugs, it is difficult to define precisely the commercial opportunity. However, the market for drugs used to treat cancer remains one of the best growth markets in the industry. Based on the ex-factory sales of 115 branded drugs, Hardman & Co estimates that growth in the global oncology market was 9.2% in 2017, and worth $121.1bn. Given the scale of

current development programmes, Hardman & Co expects the historical growth rate of 7-10% compound to be maintained for the foreseeable future and is forecasting that the oncology market will grow to $165-175bn in 2022. Even if Scancell obtained only a small percentage of this market, it would represent a very attractive return.

Valuation

Immuno-oncology continues to be one of the most attractive areas of drug development, which has been highlighted over the last month at many results meetings held by the major pharmaceutical companies. Products that have achieved a successful regulatory outcome and been commercialised, have all seen rapid uptake and generated strong sales. This suggests that Scancell's platforms will be very attractive to big pharma and/or biotech companies.

Scancell is trading on an enterprise value of ca.£34m compared with a cumulative investment of £29m to get the company to where it is today. Is this a fair reflection of the company's achievements? Certainly, another company starting out fresh today would need to spend considerably more than this to get to the same position as Scancell with two proprietary immunotherapy platforms.

Newsflow

Over the coming 18 months, Scancell is expected to have a number of noteworthy items of news that will indicate how its products are progressing, some of which will be in conjunction with its partners. Positive outcomes would represent significant valuation inflection points.

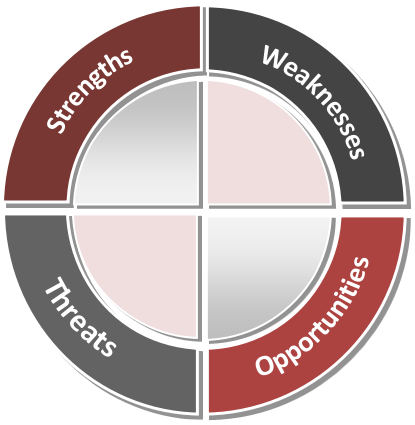
Scancell newsflow

Date	What to expect
1Q'18	Commence evaluation of Modi-specific TCRs with BioNTech
2Q'18	Submission of Investigational New Drug (IND) application for SCIB1
4Q'18	Start Phase II SCIB1 trial
4Q'18	Filing of Modi-1 Clinical Trial Application (CTA)
1Q'19	Completion of SCIB2 toxicology study
1H'19	Completion of Part 1 of SCIB1 Phase II trial
1H'19	Start Modi-1 Phase I/II trial
2H'19	Completion of Part 2 of SCIB1 Phase II trial

Source: Scancell; Hardman & Co Life Sciences Research

SWOT analysis

SWOT analysis



- Two novel disruptive technologies
- ImmunoBody – exceptional clinical outcomes
- Moditope – novel targets for vaccine therapy
- External technology validations

- Small player in competitive environment
- Drug development is capital intensive
- Commercial licensing deals take time to close

- Time and cost of clinical trials
- Competitive field; number of technologies
- Market leaders hedge position by entering into multiple deals

- Immuno-Oncology is very 'hot' area
- Platform flexibility allows targeting of several cancers
- Unfulfilled cancer market
- Big players willing to licence-in new technologies

Source: Hardman & Co Life Sciences Research

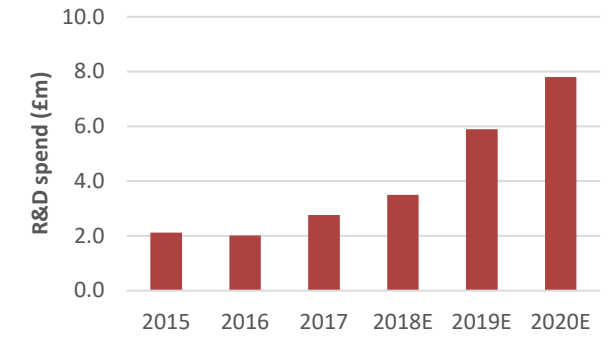
Capital requirement

Clinical development is capital-intensive. Even though Scancell has successfully obtained a partner to fund the development of SCIB2, it will require more capital to progress its other programmes. Our forecasts include a capital increase of £10m (gross) to fund the trial plans for SCIB1 and Modi-1 and general working capital purposes, which remain modest by industry standards. This would be sufficient to get the company through to a potentially important inflection point in fiscal 2020.

Investment conclusion

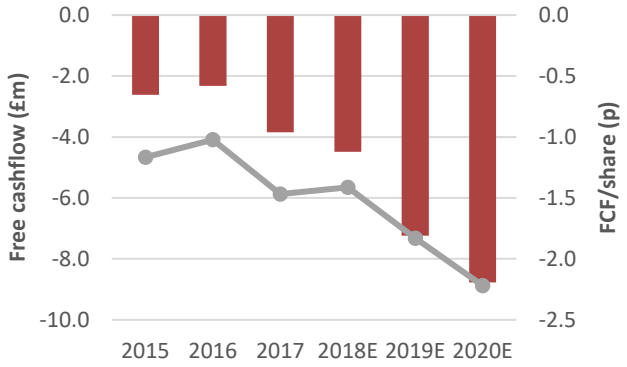
Scancell is in a strong position, with two novel immunotherapy platforms that are attracting the attention of external partners. The current enterprise value clearly does not reflect the progress that has been made by the company on very limited funds. Newsflow from trial programmes over the next 18 months could be the catalyst for further external attention, and the recent prices paid/proposed by Gilead and Celgene for the immuno-oncology companies Kite Pharma and Juno Therapeutics, respectively, highlight the potential investment returns for novel proprietary platforms/assets.

R&D investment



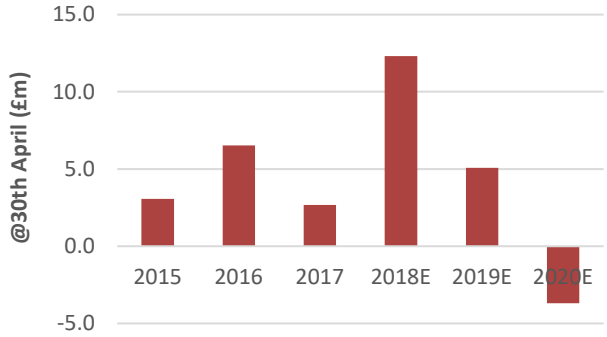
- In recent years, Scancell has invested about £2m per annum in R&D
- From 2009-18, the cumulative R&D investment has been ca.£16m, plus some additional non-equity funding
- Future investment is expected to increase significantly to take both platforms further into clinical development
- A Phase II trial for SCIB1 in combination with a CPI is scheduled to start in 4Q calendar 2018

Free cashflow



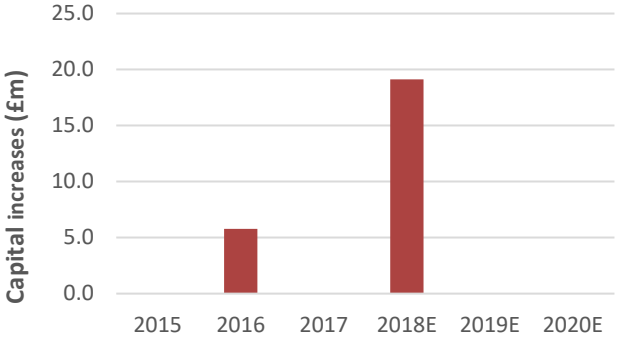
- Scancell's cash burn is related directly to R&D investment and administration costs
- There will be a modest increase in costs to prepare for the upcoming clinical trial programme
- The company has opened a US office in San Diego and an office in Oxford to coordinate US and EU clinical trials respectively

Net cash/(debt)



- At 31st October 2017, Scancell had net cash of £5.0m
- Given the planned clinical trial programme, we are assuming that the company raises up to £10m new capital during 2H fiscal 2018
- In the event that the research programmes are undertaken in line with the planned schedule, a further capital increase would be required in fiscal 2020

Capital increases



- The company has raised £23.9m through share issues since incorporation to get it where it is today
- The most recent capital increase was £5.0m (gross) to fund the preparation needed for the upcoming clinical trial programme for SCIB1, SCIB2 and Modi-1
- Our forecasts assume that Scancell will raise £10m gross new funds by the end of fiscal 2018

Source: Company data; Hardman & Co Life Sciences Research

Immuno-oncology

Immuno-oncology uses the body's own immune system to fight cancer

The immune system is programmed to recognise self from non-self. It has mechanisms in place to down-regulate itself in order to prevent normal, healthy cells from being harmed and to up-regulate if a foreign element is identified. Immuno-oncology (IO) is the use of the patient's own immune system to fight cancer.

Over the last 30 years, better understanding of both immunology and oncology has brought immense hope in the fight against cancer, and it has now become the fastest-moving segment in cancer therapy. IO is based on the principle of stimulating the patient's own immune system to recognise 'non-self' cells and to generate or increase an anti-tumour immune response in order to control or eradicate them.

If this is the case, then the question arises as to why the immune system does not successfully eliminate cancer cells on its own. There are thought to be a variety of cellular and environmental reasons why the immune system appears to be ineffective in eliminating or suppressing cancer, including:

- Difficulty discerning the difference between normal (self) cells and cancer cells.
- Not strong enough to give an effective response and eradicate the cancer cells.
- Cancer cells may produce proteins to evade detection, rendering antigen-specific cytotoxic and helper T-cells ineffective.
- Other inhibitory processes (metabolic, cytokines, suppressor cells) are present.

Three main approaches

The term 'immuno-oncology' is a general term that encompasses several different treatment approaches, each of which has a distinct mechanism of action. However, all of them are designed to boost or restore immune function in some way[1] and/or to teach the immune system to detect a foreign body. IO represents a dynamic area providing a number of target approaches, with the following three being the main focus:

- Monoclonal antibodies – including CPIs
- T-cells with engineered chimeric antigen receptors (CAR-T) or TCRs
- Therapeutic cancer vaccines/T-cell stimulators

Headlines have been associated mainly with the successes (and failures) of the different CPIs in multiple cancerous conditions, with or without chemotherapeutic agent(s), and the first approved CAR-T therapy Kymriah (Novartis) in blood cancer.

Using an active approach (i.e. produced in the body), rather than passive production (e.g. external modification and/or production of proteins, cytokines, T-cells, or monoclonal antibodies that are then administered into the body), these products work in a way more akin to the natural immune response and function within the boundaries and controls of the immune system.

Scancell has two distinct and flexible technology platforms, both in the field of therapeutic cancer vaccines, to produce high-avidity T-cell activation and anti-tumour responses.

[1] Mellman et al., Nature, 2011

Therapeutic cancer vaccines

The aim is to obtain high-avidity T-cell responses

Therapeutic cancer vaccines, or T-cell activators, are cancer cells, parts of a cancer cell or chemically pure antigens that prompt an increased immune response in the patient's body. They stimulate the immune system to produce cytotoxic T-cells which attack cancer cells that have those antigens with the expectation that this will lead to improved survival. Historically, the development of therapeutic cancer vaccines has been hampered by high failure rates that can be attributed, in part, to their failure to generate a high-avidity anti-tumour T-cell response.

It is important to note that the primary goal of a therapeutic vaccine is to generate an active immune response against an existing cancer, whereas a preventative vaccine is targeted usually at infectious diseases and aims to prevent disease from occurring in the first place.

Regulatory approved cancer vaccines

Preventative	Therapeutic
Cervarix – cervical cancer	Imlygic – melanoma
Engerix-B – hepatitis B	Provenge – prostate cancer
Gardisil – cervical cancer	
Recombivax – hepatitis B	

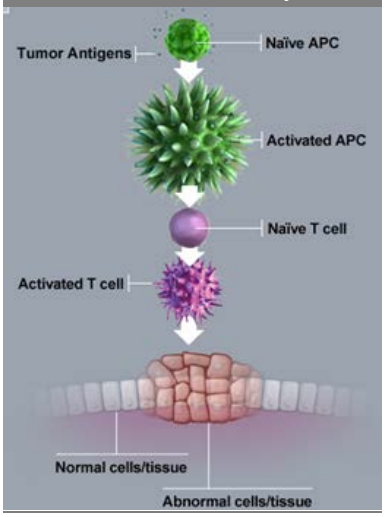
Source: Hardman & Co Life Sciences Research

There are only two therapeutic cancer vaccines on the market

To date, there have been only two therapeutic cancer vaccines approved by the regulators – Provenge (Dendreon) and Imlygic (Amgen). Provenge is designed to boost the immune system to attack prostate cancer cells. It uses an autologous approach and is, therefore, customised for each patient – white blood cells are collected from the blood and sent to a lab, where they are exposed to a protein from prostate cancer cells. The engineered cells are then reinfused back into the patient. This process is undertaken three times by each patient, which is time-consuming and expensive.

In contrast, Imlygic is a genetically modified oncolytic viral therapy which, if the tumour cells have not been removed surgically, is injected directly into the lesions of patients with recurrent melanoma. Some reports suggest that the virus induces chronic abscesses, which are painful and also risk causing further metastases.

Stimulation of immune system



APC = antigen-presenting cell
Source: Abbas and Lichtman

The immune system vs cancer cells

Cancer cells can carry tumour-associated antigens (TAAs), oncofoetal antigens, and antigens that are referred to as neo-antigens, which mark cancer cells as 'abnormal' or foreign in order to trigger the immune response by killer T-cells.

- **TAAs** are made in much larger quantities by cancer cells than normal cells, or are antigens that are not normally made by the tissue in which the cancer developed (for example, antigens that are normally made only by embryonic tissue but are expressed in an adult cancer). They alert the immune system to the dysregulated tissues.
- **Newly formed antigens** (neo-antigens) result from gene mutations in cancer cells and then are viewed as foreign by the immune system
- **Modified neo-antigens** result from enzymes that are triggered by cellular events (e.g. stress) to alter amino acids which rapidly alert the immune response

However, several factors may make it difficult for the immune system to target growing cancers for destruction:

- Many cancer-associated antigens are only slightly altered versions of self-antigens and therefore may be hard for the immune system to recognise (self-tolerance).
- Cancer cells may undergo genetic changes that may lead to the loss of cancer-associated antigens or the ability to present them and then evade the immune response.
- Cancer cells can also evade anti-cancer immune responses by providing an immuno-suppressive environment by secreting immuno-suppressive messengers like cytokines or activating negative regulatory pathways such as immune checkpoints.

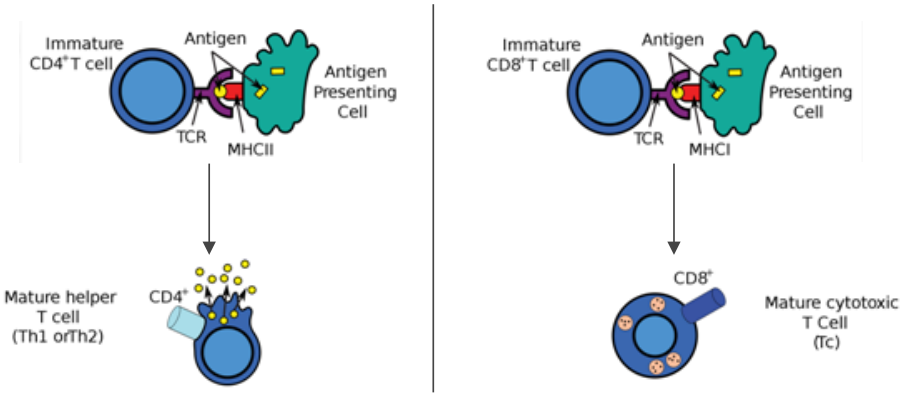
Overall, the development of cancer vaccines is a new field in the weaponry against cancer, which is where Scancell's activities are focused.

Difference between CD4 and CD8 killer T-cells

The potency of T-cells is measured by avidity or the ability to recognise low amounts of antigen processed and presented on the tumour cell surface by molecules known as major histocompatibility complex (MHC) antigens. As tumour cells generally express very low levels of any one peptide:MHC combination, it is necessary to generate high-avidity T-cells to allow recognition and lysis of tumour cells.

There are two types of MHC molecules, class I and class II, which present peptides to $CD8^+$ and $CD4^+$ T-cells, respectively. Traditionally, $CD8^+$ T-cell responses have been described as cytotoxic, or killer, T-lymphocyte (CTL) responses and it has long been known that these elements of the cellular immune response are capable of specifically recognising and destroying tumour cells. Similarly, $CD4^+$ T-cell responses are often described as helper T-cell responses because they 'help' the activity of other immune cells by releasing cytokines and can either suppress or regulate immune responses.

CD4 and CD8 T-cells



Source: adapted from www.biology.stackexchange.com

However, $CD4^+$ T-cells with cytotoxic activity have also been observed in various immune responses. These cells are characterised by their ability to recognise and kill target T-cells where specific peptides are presented on the cell surface by MHC class II molecules (rather than MHC class I, as in the case of $CD8^+$ killer T-cells).

Scancell's Moditope technology targets killer $CD4^+$ T-cells, whereas its ImmunoBody technology targets killer $CD8^+$ T-cells – the two technologies are therefore distinct and differentiated, working by two effective, but different, mechanisms.

Moditope

The approach taken with Moditope exploits a survival mechanism used by cancer cells

Moditope represents a completely new class of potent and selective immunotherapy agent which exploits a mechanism that cancer cells use to survive. It targets the modified self-antigens induced by cellular stress. Essentially, this flexible technology will allow Scancell to develop more universal cancer treatments.

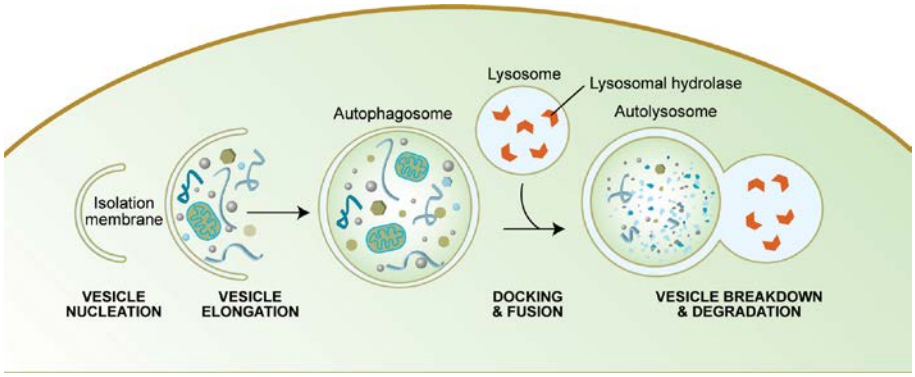
Interest in this novel vaccine approach has gained traction following the acquisition of Padlock Therapeutics by Bristol-Myers Squibb in March 2016 for up to $600m, representing up to a 30x return for shareholders over a two-year period. Padlock was focused on the use of small molecule inhibitors of citrullination for rheumatoid arthritis, whereas Scancell is applying the inverse approach of enhancing the immune response to citrullinated antigens for cancer immunotherapy.

Cancer and citrullination

Autophagy is the orderly way that T-cell components are degraded and recycle and is upregulated during cancer progression…

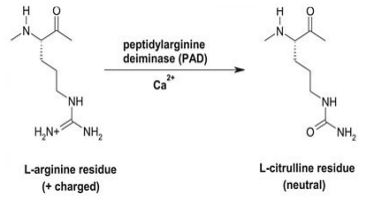
A key characteristic of cancer cells is their ability to divide rapidly, and this process requires a constant supply of nutrients in order for the cells to survive and proliferate. One of the tools used by cancer cells to promote their survival is the natural autophagy mechanism by which cellular components are degraded in an orderly manner and then recycled. This process is essential for growth regulation and the maintenance of homeostasis.

Autophagy – schematic diagram



Source: www.wormbook.org

PAD-mediated citrullination



Source: Hardman & Co Life Sciences Research

With this process, cancer cells digest and modify some of their own proteins through an important set of enzymes: the peptidyl arginine deaminases (PADs). The calcium-dependent hydrolase converts an arginine to its corresponding citrulline, a process known as citrullination, which is the conversion of the positively charged aldimine group (=NH) of arginine to the neutrally charged ketone (=O) of citrulline. The direct effect of citrullination is deactivation of protein by the modification of the 3D shape and charge of the original protein.

…but tumours are able to suppress the immune system

The immune system detects these modified proteins and triggers the $CD4^+$ T-cells around the body to search out and destroy the cancerous cells that are expressing these modified peptides. However, one characteristic of the tumour cellular environment is its ability to be immunosuppressive: T-cells are inhibited, and the tumour cells continue to grow and metastasise. Several mechanisms have been described by which tumours can suppress the immune system.

- Secretion of cytokines.
- Alterations in antigen-presenting cell subsets.
- Co-stimulatory and co-inhibitory molecule alterations.
- Altered ratios of regulatory T-cells (Tregs) to effector T-cells.

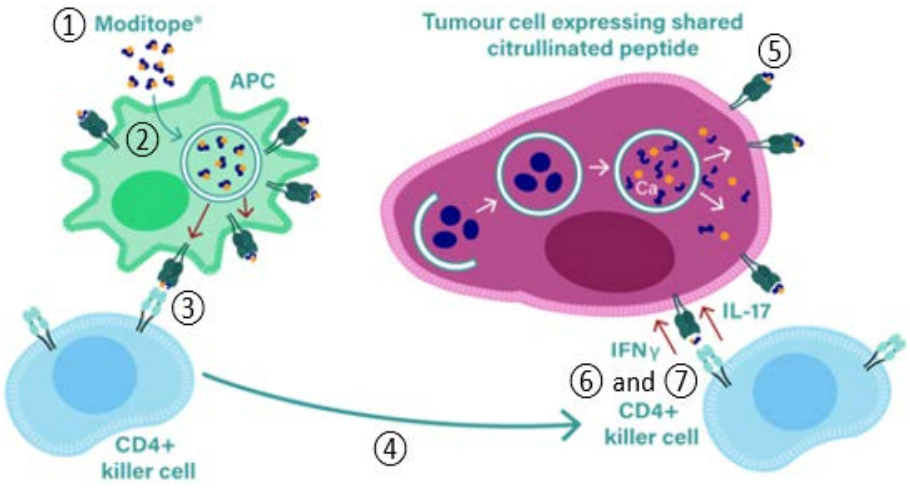
$CD4^+$ T-cells are the orchestrators of the immune response and, when activated within a tumour, release interferons (IFNs) that can reverse the immunosuppressive environment and can act directly to upregulate MHC expression on antigen presenting cells (APCs), and stimulate the release of pro-inflammatory chemokines to promote further the immune response. The autophagy process activates a cascade of events that ultimately presents citrullinated peptides on MHC class II molecules, which will trigger the immune response via $CD4^+$ T-cells.

Moditope technology

Moditope exploits the normal immune response to 'stressed' cells

Scancell has identified and patented a series of modified epitopes that stimulate the production of killer $CD4^+$ T-cells that destroy tumours without toxicity. The Moditope immunotherapy platform is based on exploiting the normal immune response to stressed cells, which is largely mediated by $CD4^+$ T-cells, and harnessing this mechanism to eradicate cancer cells by immunising with citrullinated peptides.

Moditope – mechanism of action



Source: Scancell; Hardman& Co Life Sciences Research

1. Citrullinated peptides (Moditope) are injected
2. Moditope peptides are taken up by the APCs
3. APCs present the peptides to $CD4^+$ killer T-cells
4. Primed $CD4^+$ killer cells enter the tumour
5. Stressed tumour cells undergo autophagy and express citrullinated peptides which are taken up by the APCs
6. $CD4^+$ T-cells recognise citrullinated epitopes presented by APCs and release IFNγ at the tumour site – this induces MHC class II expression on the tumour cells
7. Primed $CD4^+$ killer T-cells destroy the cancer cells expressing shared citrullinated peptides

In February 2018, the European Patent Office announced its intention to grant Scancell's application for a European patent for its Moditope immunotherapy platform. This case is key to the protection of the company's pipeline of Moditope vaccines for the treatment of cancer and will provide commercial exclusivity in all major European territories. Counterparts to this patent have been filed in Australia, Brazil, Canada, China, Hong Kong, Japan, South Korea, South Africa and the US.

Modi-1

Modi-1 contains two citrullinated vimentin epitopes and one citrullinated epitope from α-enolase

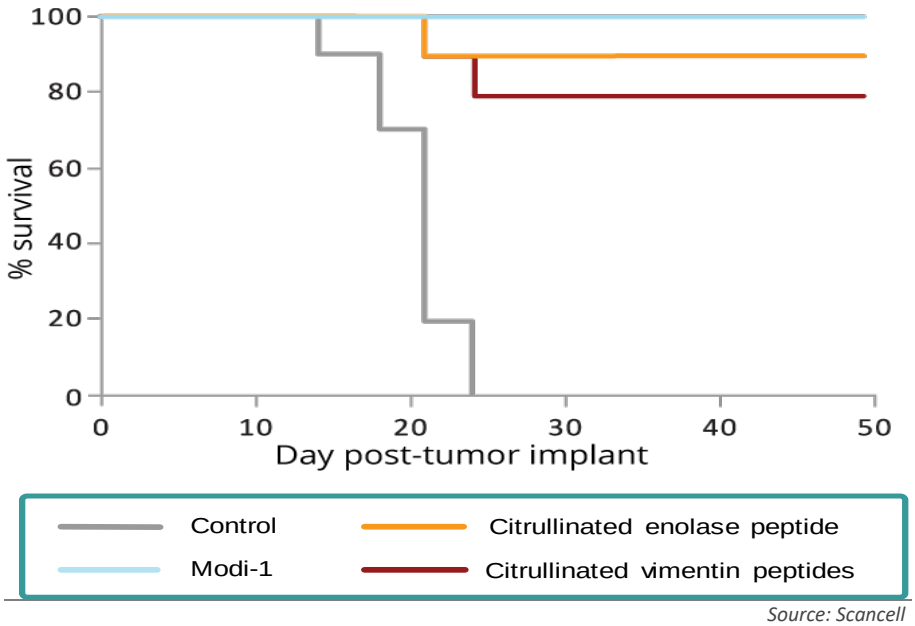
Scancell's lead product using Moditope technology, Modi-1, is a combination of two citrullinated vimentin peptides (Vim-1 and Vim-2), plus one citrullinated α-enolase (Eno-1) epitope. These epitope targets are known to be highly expressed in triple negative breast cancer (90%), ovarian cancer (95%) and sarcoma (100%). With Modi-1, Scancell aims to treat patients with large and bulky tumours that do not respond to other therapies and who have poor prognosis.

In vivo pre-clinical study

In vivo pre-clinical studies produced 100% survival rates

The following graph shows the results from an *in vivo* study on tumour-bearing mice (B16 tumour cells expressing the MHC molecule HLA-DR4 under the influence of an IFNγ inducible promoter).

Moditope *in vivo* study

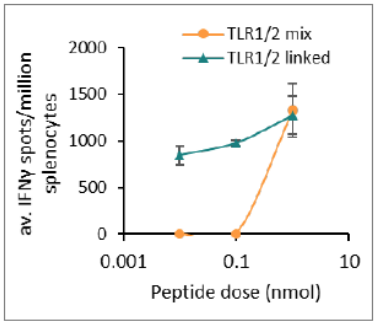


Source: Scancell

The results show an excellent overall survival against this aggressive tumour cell line up to 50 days after the mice received a single immunisation with citrullinated vimentins or citrullinated α-enolase, with survival rates of 80% and 90%, respectively. However, the combination of all three citrullinated peptides that constitute Modi-1 generated the best result, with 100% survival up to 50 days after being implanted, with no associated toxicity.

These data demonstrate how Modi-1 can mediate a potent anti-tumour response through $CD4^+$ T-cells against citrullinated epitopes on tumour cells. In addition, they illustrate for the first time, how citrullinated peptides produced during autophagy may offer attractive targets for cancer therapy. Due to the reversal of the immunosuppressive tumour environment, there is no longer any need to add a CPI, offering a completely new approach in immunotherapy.

Modi-1 linked adjuvant



Source: Scancell

Progress in Modi-1

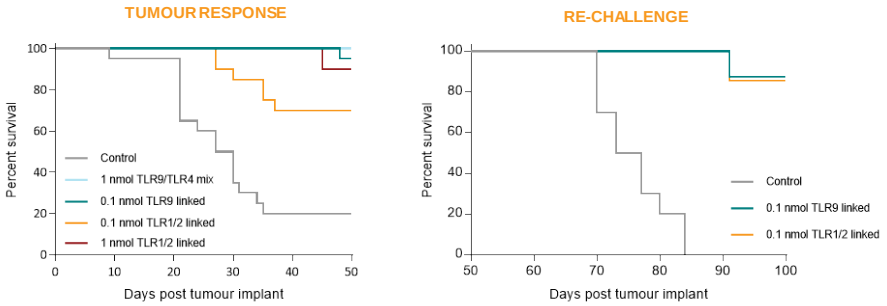
Substantial progress has been made recently with the Modi-1 vaccine following identification of an adjuvant (toll-like receptor agonist) that could be covalently linked to the Moditope peptides. This resulted in enhanced levels of cancer-killing T-cells, which, in turn, allows a 10 to 100-fold reduction in dose compared with the original version of Modi-1.

Scancell is close to initiating GMP manufacture of Modi-1 conjugated to the TLR-based adjuvant with the aim of filing a clinical trial application (CTA) in the UK for the planned Phase I/II clinical trial prior to starting the study in 1H calendar 2019.

Modi-1 and cancer recurrence

Additional *in vivo* data show that immunisation with Modi-1 induces memory responses after re-challenge and prevent cancer recurrence. Animals surviving the first challenge with tumour cells are re-challenged with new tumour cells 50 days after their original challenge; almost all animals survived this second challenge showing that they had a memory response.

Modi-1 prevents cancer recurrence in murine model



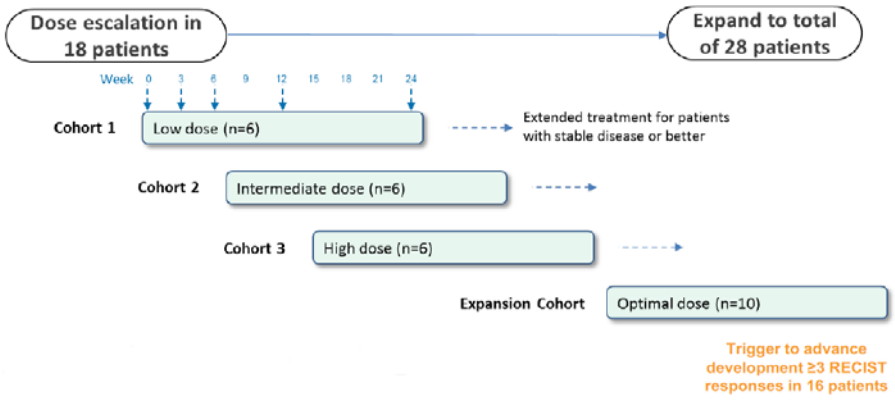
Source: Scancell

Planned Modi-1 proof-of-concept trial

Modi-1 proof-of-concept study to start in 2019

The next stage in the development of Modi-1 will be a proof-of-concept trial in humans. Scancell is aiming to start a Phase I/II trial in early 2019 on 28 patients with triple negative breast cancer, ovarian cancer, and sarcoma who have failed or become intolerant to all other conventional therapies. Initial readout of safety and efficacy data is anticipated during 1H'20. The anticipated cost of undertaking this trial is expected to be in the region of £3-4m.

Modi-1 first in human trial

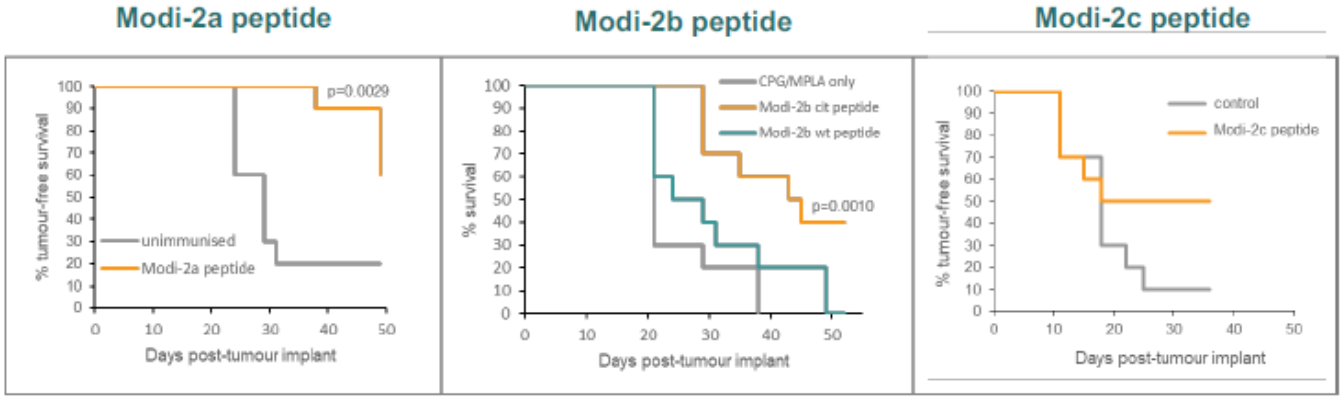


Source: Scancell

Modi-2

The second product using the Moditope platform is targeting a broad range of solid tumours. The development candidate, Modi-2, is a combination of three undisclosed citrullinated peptides that are highly expressed in many solid tumours. In pre-clinical studies, a single immunisation by each citrullinated Modi-2 peptide has been shown to prolong significantly the survival rates. Scancell is aiming to start pre-clinical development of selected epitopes during 2018.

Development candidate – Modi-2



Source: Scancell

Initially, Modi-2 will address cancers resistant to CPI therapy, including oesophageal, gastric, pancreatic and colorectal cancers.

BioNTech research collaboration

Research collaboration

In January 2018, Scancell received a strong endorsement of its Moditope platform when it entered into an important research collaboration with BioNTech, one of Europe's leading immuno-oncology companies. This new partnership will investigate the potential for developing T-cell receptor-based therapies for the treatment of cancer. The initial research focus is to identify and characterise TCRs specific for the citrullinated Modi-1 epitopes. Engineering T-cells to express these CD4-specific TCRs would represent a novel form of personalised cell therapy for treating cancer.

BioNTech

Scancell has attracted a sound partner in personalised medicine which represents a strong validation for its technology. Founded in 2008, BioNTech has become Europe's biggest privately-held biopharmaceutical company. It has a strong focus on the development of targeted and personalised mRNA vaccines and immunotherapies, ranging from innovative CAR-T and TCR-based products to novel antibody checkpoint immunomodulators and small molecules.

Since inception, BioNTech has attracted strong partners, notably Roche/Genentech, Eli Lilly, Sanofi, and Genmab, with deals worth nearly $1bn, the most recent being a $310m deal with Roche to test BioNTech's m-RNA vaccine in combination with Roche's recently launched CPI, Tecentriq (2017 sales $495m). In January 2018, BioNTech raised $270m of Series A financing with the proceeds being earmarked to further advance its clinical pipeline of individualised immunotherapies. The new money will also be used to conduct more clinical trials in multiple types of cancer.

T-cell receptor therapy

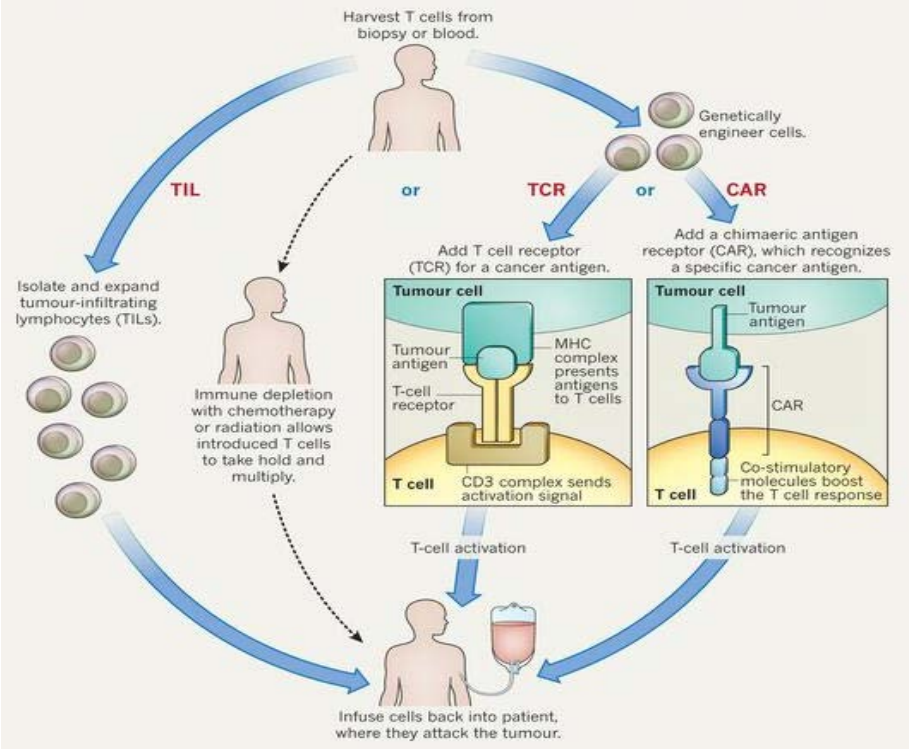
TCR therapy has the potential to challenge difficult-to-penetrate solid tumours and overcome the tumour-suppressive microenvironment, which seems difficult for CAR-T therapies to achieve. This form of therapy is highly targeted and personalised, and aims to harness the cytotoxic and other immunomodulatory capabilities of T-cells to eliminate cancers (or viral infections) without eliciting undesired side effects. TCR therapy allows the direct detection of the processed tumour antigen when it is presented by MHC molecules on the cancer cell surface.

Although it may be possible to isolate T-cells for viral targets, the process is more challenging in cancer as most TAAs are derived from self-antigens and, therefore, are poorly immunogenic. In addition, the tumour's immunosuppressive environment protects itself from immune attack.

The novelty of the Scancell/BioNTech approach is that it will focus on identifying CD4-specific TCRs that recognise the citrullinated Modi-1 neo-epitopes that are upregulated on cancer cells, rather than CD8-specific TCRs that recognise TAAs or other normal proteins over-expressed by cancer cells.

Despite the challenges of identifying and isolating TCRs recognising TAAs, TCR therapy is one of the three main approaches being adopted for personalised cancer treatment, the others being CAR-T and Tumour-Infiltrating Lymphocytes (TILs), as illustrated in the schematic below.

Activated T-cells – mode of action



Source: C. Humphries, Nature Cancer Immunotherapy, 2013, 504, S13-S15

There has been a lot of M&A activity involving TCR therapy, exemplified by the acquisition of Kite Pharma (which was, among other projects, developing a TCR programme in solid tumours) by Gilead in August 2017 for nearly $12bn, to gain a leading position in cellular therapy. In addition, Celgene is in discussions with Juno, which is also developing CAR-T and TCR therapies, for about $9bn.

CRUK Grand Challenge

Member of high-profile team shortlisted for award

CRUK's Grand Challenge is a series of £20m awards seeking international, multidisciplinary teams willing to take on the toughest challenges in cancer – providing the freedom to try novel approaches, at scale, in the pursuit of life changing discoveries.

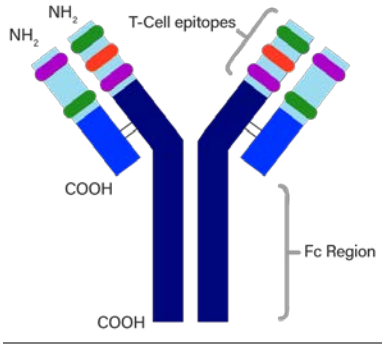
Scancell announced recently that a multi-disciplinary team of leading cancer immunotherapy scientists in Europe and the US, led by Professor Lindy Durrant, CSO of Scancell, and in partnership with Genentech, BioNTech and ISA Pharmaceuticals, has been shortlisted from over 130 applications to the final stages of CRUK's Grand Challenge. The team will collaborate on a project entitled: "*Project Blueprint: Eradicating established tumours with unique cancer vaccines*".

The team aims to investigate the full potential of the tumour vaccine concept by building blueprints for an effective therapy for patients with most types of cancer. The project focus will be on head and neck cancer, glioblastoma, lung and pancreatic cancer – all of which currently have a poor prognosis – in which treatment with Modi-3, another product generated from Scancell's Moditope platform, will be assessed alongside vaccines targeting new mutations within individual patients' tumours.

Being an integral member of this global team shortlisted for such a prestigious award provides further external validation of the Moditope technology and exemplifies the strong science behind Scancell's approach to tumour therapy.

ImmunoBody

ImmunoBody antibody

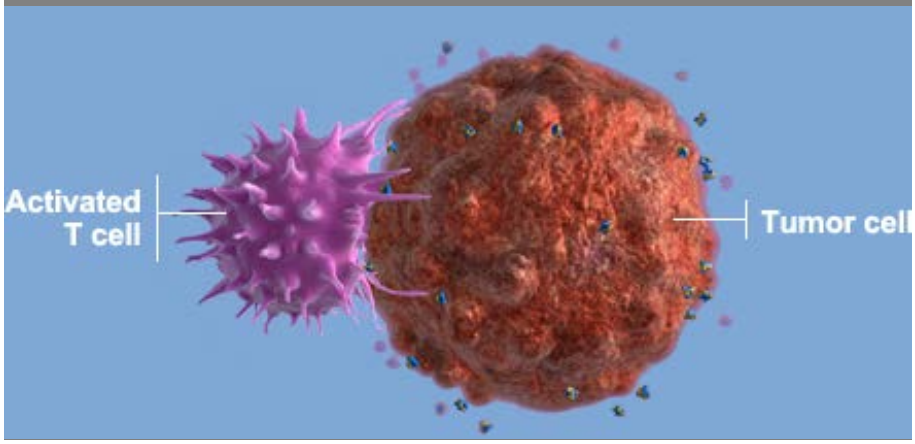


Source: Scancell

Scancell's ImmunoBody technology generates high-avidity tumour-killing $CD8^+$ T-cell responses that target and eliminate tumours with a magnitude superior to that generated by currently approved vaccines. Each ImmunoBody therapeutic vaccine can be designed and customised to target a particular cancer in a highly specific manner. It also offers the potential for enhanced avidity of the T-cell response, resulting in greater efficacy and improved safety compared with more conventional approaches.

An ImmunoBody is a DNA plasmid that encodes a human antibody engineered to express epitopes from tumour antigens over-expressed by cancer cells. Antibodies are ideal vectors for carrying T-cell epitopes to tumour antigens as they have a long half-life and can target dendritic cells via their Fc receptors, allowing efficient stimulation of both helper and CTL responses. The helper T-cells overcome the immunosuppressive tumour environment and greatly increase the population of killer $CD8^+$ T-cells, which attack the tumour site. As described above, the potency of T-cells is measured by avidity or the ability to recognise low amounts of antigen processed and presented by MHC molecules. As tumour cells express very low levels of any one peptide:MHC combination, it is necessary to generate high-avidity T-cells to allow recognition and tumour lysis.

Activated T-cells – mode of action



Source: www.fightcancerwithimmunotherapy.com

Features

- Multiple tumour 'target antigens' (T-cell epitopes) that are engineered into a single antibody framework.
- Customisation and targeting different tumour types can be achieved by grafting different T-cell epitopes into the framework.
- The vehicle is efficiently taken up by cells involved in triggering T-cell responses (antigen-presenting cells) by the antibody tail (Fc region).
- ImmunoBody can be delivered as a DNA plasmid that is flexible, easy to manufacture and relatively inexpensive.

The ImmunoBody structure is able to incorporate up to six different T-cell epitopes. If the epitopes are nested, then this could be increased further. Therefore, ImmunoBody could target multiple antigens and be recognised in all common human leukocyte antigen (HLA) types.

The major advantage of the ImmunoBody technology is that the Fc (constant region) component of the engineered antibody will be recognised by the high affinity CD64 receptor present on activated APCs. The antibody is then internalised and processed by the APC, resulting in a significant enhancement of both the frequency and avidity of the T-cell immune response. Previous studies have shown that Fc receptor internalisation of antigen-antibody complexes is 1,000-fold more efficient than pinocytosis for stimulation of helper T-cell responses.

Scancell is developing two products using its ImmunoBody platform – SCIB1 and SCIB2. This platform has great flexibility, whereby epitopes targeting one type of cancer can be swapped for epitopes targeting another type of cancer, thus creating a different DNA vaccine.

SCIB1 and SCIB2 ImmunoBodies

ImmunoBody	SCIB1	SCIB2
Indication	Malignant melanoma	Non-small cell lung cancer (NSCLC)
Stage	Phase I/II	Pre-clinical
Description	SCIB1 ImmunoBody encodes two CD8 epitopes from the melanoma antigens TRP-2 and gp100 plus two CD4 epitopes from gp100	SCIB2 ImmunoBody encodes 16 NY-ESO-1 T-cell epitopes

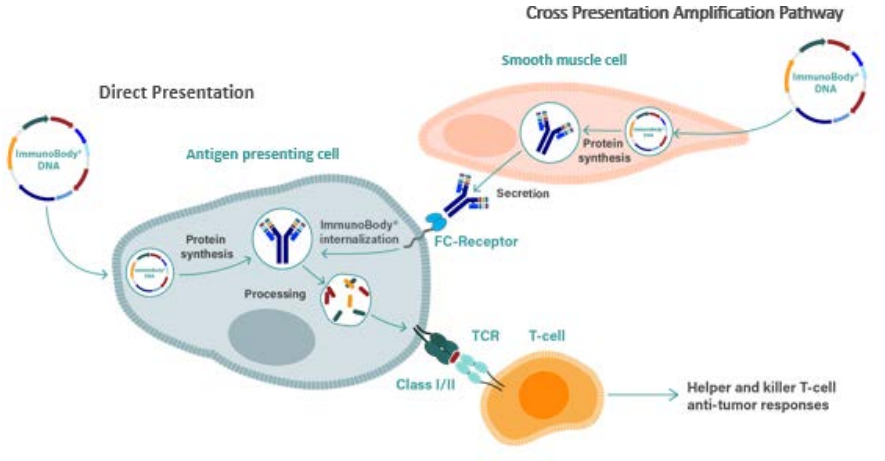
Source: Hardman & Co Life Sciences Research

Dual mechanism of action of ImmunoBody

Two presentation mechanisms work synergistically to produce 100x greater T-cell responses

The combination of direct and cross presentation by ImmunoBody results in amplification of the immune response, inducing high-frequency, high-avidity T-cells that deliver a potent anti-tumour effect.

ImmunoBody – dual mechanism of action



Source: Scancell

Direct presentation

Direct presentation produces only moderate avidity T-cell avidity…

The ImmunoBody DNA targets APCs directly via transfection. The DNA is transcribed, translated, and then the antibody is processed. The tumour-specific T-cell epitopes are presented via the MHC class I and II molecules to $CD8^+$ and $CD4^+$ T-cells, respectively. However, the immune response generates only moderate T-cell avidity, which is too weak to produce a strong anti-tumour effect in an immunosuppressed environment.

...and so does cross presentation...

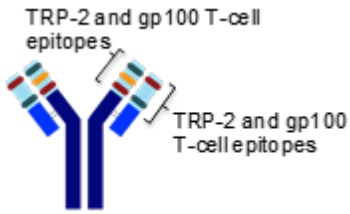
Cross presentation amplification pathway

The ImmunoBody DNA also transfects other (non-APC) cells, which then secrete the antibody protein that targets APCs' CD64 receptors via the high-affinity Fc component. The antibody is internalised and cleaved, and the epitopes are presented via the MHC molecules to the $CD4^+$ and $CD8^+$ T-cells. As in the previous mechanism, the immune response gives a low T-cell avidity which is too weak to trigger an effective anti-tumour response. However, the synergistic effect of the dual mechanism of action (direct plus cross presentation) is to produce 100x greater T-cell responses compared with either presentation alone.

SCIB1

Unprecedented patient outcomes with SCIB1

SCIB1



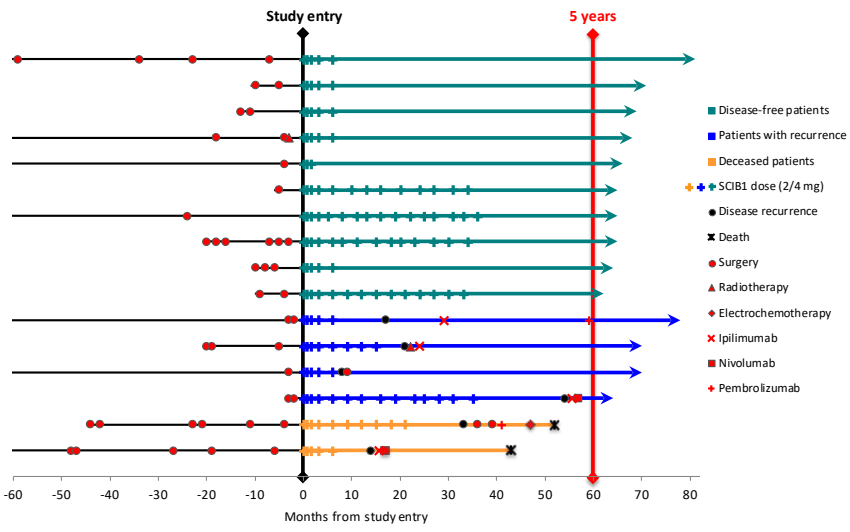
Source: Scancell

Scancell's lead candidate using the ImmunoBody platform is SCIB1, which induces T-cells with sufficient avidity to cause tumour regression in patients with melanoma. In a Phase I/II trial, patients with resected (n=20) or inoperable stage III and stage IV melanoma (n=15) were recruited. Stage III melanoma is a cancer that has spread to the regional lymph nodes but has not yet spread to distant lymph nodes or to other parts of the body (metastasised), while stage IV melanoma has.

The company announced in February 2018 that data from the Phase I/II trial had been published in the peer-reviewed journal *Oncoimmunology*. The conclusions of the study were that "SCIB1 is a novel class of anti-cancer immunotherapy that induces T-cells which can cause tumour regression in patients with melanoma. The high frequency of responses, their breadth and durability suggest that SCIB1 is worthy of further study in a larger cohort of patients. This is particularly the case in the adjuvant setting, where all of the patients responded immunologically and where absence of toxicity is an important clinical consideration. Furthermore, the stimulation of potent *de novo* immune responses by SCIB1 may provide an opportunity for synergistic combination therapy with CPIs in late stage disease."

Five-year survival data

Five-year survival 'swimmer plot'



Source: Scancell

Since the cut-off date for the publication, the company has continued to collect survival data for the trial patients. Of the 20 patients who had their tumours resected prior to SCIB1 treatment, 18 are still alive. Of the 16 resected patients who received the lower dose of SCIB1 (2-4 mg), 14 are still alive and have all now passed the five-year time point, as demonstrated in the 'swimmer plot' presented above. Each line corresponds to a patient with annotations of events associated with the respective disease.

Six of the 16 patients saw recurrence of the disease including two deaths, bringing the five-year overall survival (OS) to 87.5% and the recurrence free survival (RFS) to 62.5%. Interestingly, despite having received multiple interventions and recurrences prior to study entry, 10 patients had no recurrence yet only received SCIB1 therapy. These results have to be considered in parallel with published results of the five-year OS at 40-78% and 15-20% for stage III and IV melanoma, respectively[2], and the five-year RFS of 28-44% for stage III melanoma[3].

SCIB1 survival comparisons

Trial	SCIB1	---------- Published data ----------	
Melanoma stage	III/IV	III	IV
Overall survival	87.5%	40-78%	15-20%
Recurrence-free survival	62.5%	28-44%	-

Source: Published literature; Scancell; Hardman & Co Life Sciences Research

These results show the overall superiority of SCIB1 compared with the standard of care with unprecedented OS and RFS for these late-stage melanoma patients. In addition, no serious adverse event occurred during the study – in contrast to the CPIs, which, despite prolonging the time before disease recurrence, see patients discontinuing treatment due to adverse reactions.

Combination of SCIB1 with a PD-1 checkpoint inhibitor

Rationale

Scancell expects SCIB1 to improve the clinical outcomes of checkpoint inhibitors

Although the SCIB1 trial showed that resected patients with low tumour burden responded well to therapy, patients with more advanced disease may benefit from using this drug in combination with a CPI. Checkpoint blockade has been demonstrated to produce anti-tumour responses in approximately 20-40% of melanoma patients. However, the majority of patients are non-responders and do not stimulate a sufficiently large immune response against their tumours to eradicate them. These patients could benefit from an effective vaccine that stimulates high-avidity T-cell responses in combination with checkpoint blockade.

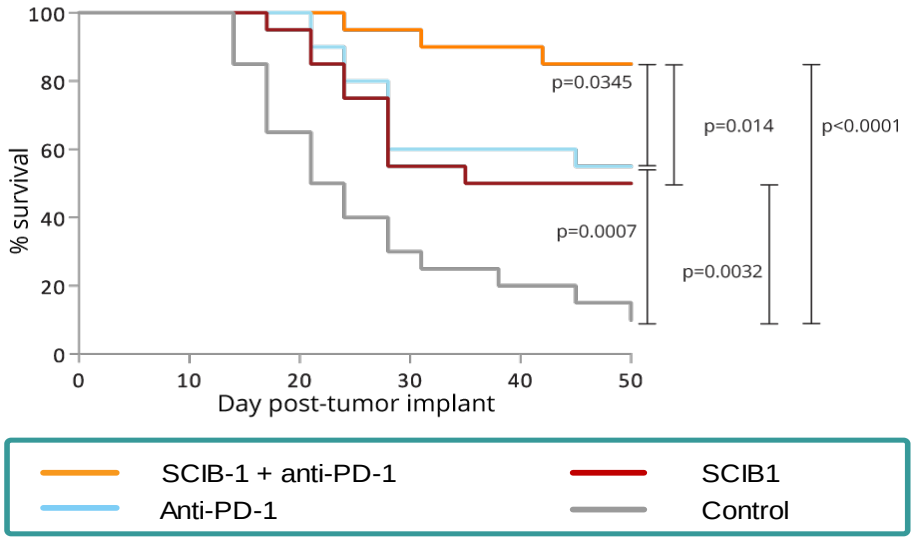
This is not a totally new concept, but outcomes are dependent on the efficacy and synergistic activity of the underlying drugs. For example. Bristol-Myers Squibb undertook a Phase III trial with MDX-1379 (2 x gp100 peptides) in combination with ipilimumab (CTLA-4 inhibitor), and showed that this vaccination did not generate T-cells with sufficient avidity to eradicate the tumours.

In contrast, in an *in vivo* pre-clinical study, with the vaccination of HLA-DR4 transgenic mice with SCIB1 induced high-avidity T-cell responses which resulted significantly improved survival rates. However, the use of SCIB1 in combination with a CPI improved survival rates to 85%.

[2] CRUK data

[3] F. Costa Svedman et al *Clin.Epidemiol*. **2016**, 8, 109-122.

Comparison of SCIB1 alone or with PD-1 antibody

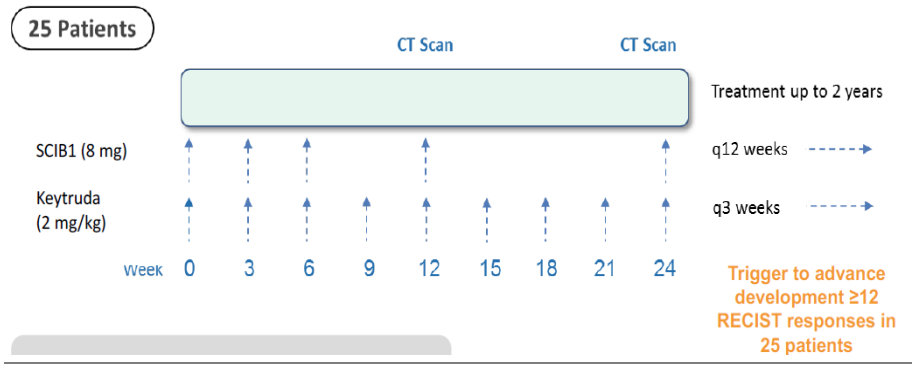


Source: Scancell

Design of Phase II combination trial

The Phase II study will investigate the use of SCIB1 in combination with pembrolizumab (Keytruda) in patients with unresectable stage III or IV melanoma. Initially, the safety and tolerability of SCIB1 in combination with the anti-PD-1 antibody will be assessed in a small cohort of patients (n=6) and, on the back of a positive outcome, efficacy and safety will be assessed in a further 19 patients (total = 25). The primary end-point will be the overall tumour response rate, with secondary end-points including the immune-related response rate, duration of the response and progression-free and overall survival at 12 months. The trial will be led by Dr Flaherty (Harvard Medical School, US).

SCIB1 + PD-1 Phase II trial protocol



Source: Scancell

The expectation is that such a combination will increase the response rate from around 30% with pembrolizumab alone to at least 50% with the combined treatment.

Scancell aims to submit the IND application using SCIB1 in combination with an anti-PD-1 CPI to the FDA during 2Q 2018. The study will use the new electroporation delivery device, TriGrid 2.0 from Ichor. The FDA recommended that Ichor submits its Master File dossier 30-60 days prior to Scancell's own submission, and this has now been done.

Following submission of the IND application and, subject to sufficient funding being available for the trial, patient enrolment is anticipated to commence in 4Q 2018, with preliminary efficacy and safety read-out by the end of 1H 2019 and completion of the second part of the study 12 months later (1H 2020).

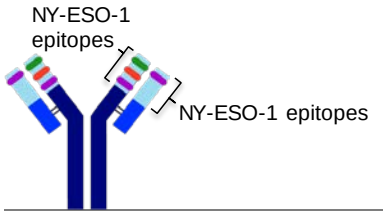
Orphan Drug status

The Orphan Drug Designation programme provides orphan status to drugs and biologics, which are defined as those intended for the safe and effective treatment, diagnosis or prevention of rare diseases/disorders that affect fewer than 200,000 people in the US, or that affect more than 200,000 persons but are not expected to recover the costs of developing and marketing a treatment drug.

In February 2014, the FDA granted SCIB1 Orphan Drug Designation for the treatment of metastatic melanoma. The terms allow Scancell a 50% tax credit for clinical trials, a waiver of the prescription drug user fee when the filing is made and a period of seven years of market exclusivity following drug approval. During this period, the FDA will not approve a New Drug Application or a generic drug application for the same product.

SCIB2

SCIB2



Source: Scancell

SCIB2 uses the ImmunoBody platform to target tumours expressing the highly immunogenic NY-ESO-1 antigen, a validated cancer target. NY-ESO-1 has restricted expression in normal cells and is over-expressed in tumour cells – particularly, NSCLC (18%), prostate (39%), and bladder cancer (35%) patients. A variety of vaccination approaches targeting NY-ESO-1 have been tried using synthetic peptides, recombinant proteins and DNA encoding full-length NY-ESO-1, but they have all failed to induce high enough T-cell avidity to control tumour growth. In contrast, SCIB2 is designed to generate high-avidity T-cell responses. On the back of the unprecedented patient outcomes from the SCIB1 trial, supported by pre-clinical studies, Scancell planned a proof-of-concept Phase II trial in NSCLC patients. However, commencement of this trial was dictated largely by Scancell's ability to raise the necessary funding, estimated by Hardman & Co to be ca.£5m.

Partnership with CRUK

In December 2017, Scancell signed a Clinical Development Partnership with the charitable organisation, CRUK, whereby CRUK will fund a Phase I/II trial with SCIB2 in combination with a CPI. This represents strong validation and powerful endorsement of Scancell's ImmunoBody platform, and is a very big commitment from CRUK. Under the terms of the agreement, CRUK will:

- Fund the manufacture of SCIB2 to GMP standard.
- Undertake all the preparatory and regulatory work.
- Fund and manage the clinical trial.

Scancell secured a deal with CRUK to progress SCIB2 into Phase I/II trial, with CRUK financing and sponsoring the trial

Within this partnership, the progress of SCIB2 will benefit from having access to CRUK's extensive network of oncology specialists plus the experience of the Centre for Drug Development (CDD) in managing trials. The CDD focuses on early-stage development, dedicated to pioneering new treatments in oncology by working in partnership with academic and the biotechnology sectors.

Pre-agreed terms

Scancell has the option to acquire the data at the end of the trial…

…but also has a back-stop in the event that it decides not to exercise

Following completion of the proposed Phase I/II clinical trial, Scancell will have the option to acquire the rights to the data on pre-agreed terms in order to progress the SCIB2 programme through further development, either by itself or in a subsequent deal with a major pharmaceutical/biotech company. In the event that Scancell decides not to exercise this option, CRUK will retain the right to take the programme forward in all indications and commercialise it independently, and Scancell would be eligible to share any revenues received by CRUK.

The partnership allows Scancell to focus resources on other opportunities

Financial terms remain confidential, but we understand that, if the trial is successful, Scancell will have to pay CRUK a modest pre-agreed option fee – lower than our estimated cost of the trial – plus milestone payments and ratcheted royalties on future sales.

Trial design

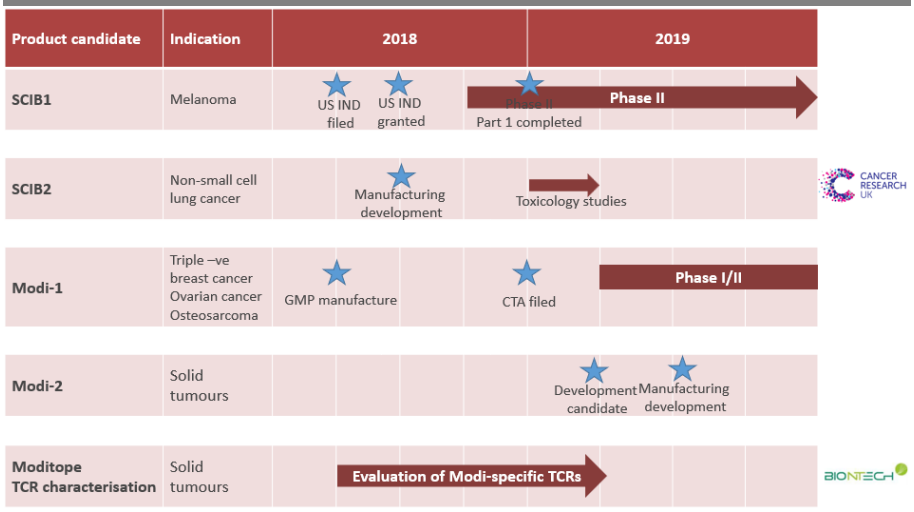
The trial will focus initially on NSCLC patients expressing the epitope NY-ESO-1, and could then be extended to other solid tumours expressing the same epitope. The CDD will decide on the size of the trials after discussion with Scancell.

R&D pipeline and timetable

Two platforms, four products, multiple indications

Scancell's two proprietary immunotherapy platforms are being developed in parallel through a pipeline of four products targeting cancers with unmet medical need; this is summarised in the following graphic.

Short term R&D milestones



Source: Hardman & Co Life Sciences Research

Over the last 12 months, the company has been preparing the groundwork for these trials to begin. Clearly, having CRUK as a partner to manage and fund the SCIB2 trial in combination with a CPI is an enormous bonus for the group, while also providing an important external endorsement of the technology. This will allow management to advance and expand further its internal projects. This programme will result in a step-change in the number of likely announcements from the company compared with last year.

Newsflow – what to expect

ImmunoBody		Moditope	
2Q'18	SCIB1 IND filing	1Q'18	GMP manufacture of Modi-1
2Q'18	Begin manufacturing development for SCIB2	1Q'18	Begin evaluating Modi-specific TCRs
4Q'18	Commence SCIB1 Phase II trial	4Q'18	File Modi-1 CTA
4Q'18	Start SCIB2 toxicology studies	1H'19	First patient treated with Modi-1
1H'19	Complete Part 1 of SCIB1 Phase II	1H'19	Modi-2 lead candidate characterised
1H'19	Complete SCIB2 toxicology	1H'19	Complete initial evaluation of Modi-specific TCRs
2H'19	Complete Part 2 of SCIB1 Phase II	1H'19	GMP manufacture of Modi-2

Source: Hardman & Co Life Sciences Research

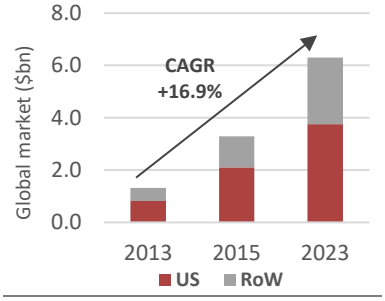
Further funds will be required to move programmes into the next stage

In order to achieve these goals, Scancell will require further funds. Based on our best estimates of the costs of early-stage clinical trials in this field, we have forecast that a cash raise in the order of £10m will be required. Such a sum would be sufficient to undertake this programme and achieve headline results in the expectation that at least one of the products will generate data that represents an important valuation inflection point and attract a commercial licensing deal, and to provide sufficient headroom for any unexpected delays.

Commercial opportunity

Melanoma: SCIB1 market opportunity

Global melanoma market



Source: Hardman & Co Life Sciences Research

Globally, the metastatic melanoma market is projected to grow with a CAGR of 16.9% from $1.3bn in 2013 to $6.3bn by 2023. In 2017, this market was estimated at $4.1bn, boosted by the rapid uptake of Opdivo (BMS). The US represents 60-65% of the global market during this period.

BMS has established itself as a key player in the checkpoint immunotherapy and melanoma market, with two of the top three best-selling drugs approved for the treatment of unresectable or metastatic melanoma. In 2011, it launched Yervoy (ipilimumab), which targets CTLA-4. Rapid uptake generated sales of $1.2bn in 2017, giving cumulative sales since launch of $6.7bn. This was followed in late 2014 by Opdivo (nivolumab), an anti-PD-1 antibody, which has rapidly become the best-selling checkpoint inhibitor drugs for melanoma (also used in other indications), with 2017 sales of $5.0bn. Competition is intense with Keytruda (pembrolizumab, Merck & Co) also targeting PD-1, achieving sales of $3.8bn following its approval in 2014.

Given that the overall response rate using CPIs is disappointing, only in the 20-40% range, there remains a significant opportunity to improve outcomes. Non-responders to immunotherapy have no further treatment options apart from the largely ineffective chemotherapy regimens. This represents the target population for SCIB1.

With 11 approved and well-established drugs used currently in melanoma, and with more than 198 open studies registered[4], Scancell would be entering a crowded market place. However, good results in the combination study, backing up those obtained in the proof-of-concept trial, would be used to entice a licensing partner to take this asset to the next stage and commercialisation in melanoma.

SCIB1, in combination with CPI, is targeting stage III/IV patients with unresectable or metastatic melanoma. While this is the same market as that being targeted by Opdivo and Keytruda, the commercial experience with these drugs demonstrates that an improvement in patient outcomes would be reflected by a rapid uptake of the product.

Marketed melanoma drugs

Drug	Name	Company	Mode of action	2017 sales
Opdivo	Nivolumab	BMS/Ono	PD-1 humanised monoclonal antibody	$4,948m
Keytruda	Pembrolizumab	Organon/Merck & Co	PD-1 humanised monoclonal antibody	$3,809m
Yervoy	Ipilimumab	BMS	CTLA-4 monoclonal antibody	$1,244m
Mekinist	Trametinib	Novartis	MEK kinase inhibitor	$473m
Tafinlar	Dabrafenib	Novartis	BRAF kinase inhibitor	$400m
Zelboraf	Vemurafenib	Roche/Genentech	BRAF kinase inhibitor	$180m
Cotellic	Cobimetinib	Exelixis/Roche	BRAF/MEK kinase inhibitor	$61m
Aldesleukin IL-2	Interleukin-2	generic	General immune system boost	N/A
DTIC-Dome	Dacarbazine	Bayer	DNA alkylating agent	N/A
Imlygic (T-vec)	Talimogene Laherparepvec	Amgen	Oncolytic virus	N/A
Intron A	Recombinant Interferon alfa-2b	Merck & Co	General immune system boost	N/A

Source: Company reports; Hardman & Co Life Sciences Research

[4] www.cancer.gov

NSCL cancer: SCIB2 market opportunity

NSCLC market

Hardman & Co estimates that the global market for NSCLC drugs treatment was $9.7bn in 2017, which represents a significant rise over the $7.0bn market estimate in 2015. Based on current estimates, the market looks set to see continued strong double-digit growth over the next five years to ca.$16.0bn, such is the unmet medical need. Although the standard of care until recently was Avastin (used also in other conditions; Roche), which dominates the overall market, with sales of $6.8bn in 2017 and cumulative sales since launch of $70.9bn, it has been joined by the two PD-1 inhibitors, Opdivo and Keytruda, which have also become widely used.

These CPIs have been approved by the FDA as single agents for the second-line therapy of patients with advanced NSCLC. Keytruda is also approved in the US for the first-line treatment of patients with NSCLC, with at least 50% of tumour cells showing PD-L1 expression, and in combination with carboplatin and pemetrexed as first-line treatment for patients with metastatic NSCLC regardless of PD-L1 status. In the UK, Keytruda has also been recommended (January 2017) by the National Institute for Health and Care Excellence (NICE) as an option for treating locally advanced or metastatic PD-L1-positive NSCLC. At this time, assessment of the cost-benefit of Opdivo is in progress by NICE and, consequently, it is not yet recommended for use in the UK.

Despite these recent approvals, there remains an unmet need to develop a treatment for these patients that results in improved response rates. In the population approved to receive Keytruda for NSCLC in the UK, there are still ca.80% of patients unlikely to respond. Therefore, there is a strong rationale for investigating the effect of inducing tumour-specific, high-avidity, killer T-cells in NSCLC patients being treated in combination with checkpoint blockade.

Ranking drugs approved for NSCLC

Rank	Brand name	Generic name	Company	Mechanism of action	2017 sales	Cumulative
1	Avastin	Bevacizumab	Roche	VEGF recombinant human mAb	$6,797m	$70,888m
2	Opdivo	Nivolumab	BMS	PD-1 humanised mAb	$4,948m	$9,670m
3	Alimta	Pemetrexed	Eli Lilly	Folate antimetabolite	$2,063m	$24,531m
4	Afinitor	Everolimus	Novartis	mTOR inhibitor	$1,525m	$9,086m
5	Abraxane	Paclitaxel	Abraxis/Celgene	Anti-mitotic	$992m	$5,314m
6	Tagrisso	Osimertinib	AstraZeneca	EGFR kinase inhibitor	$955m	$1,397m
7	Tarceva	Erlotinib	Roche	EGFR kinase inhibitor	$857m	$14,239m
8	Cyramza	Ramucirumab	Eli Lilly	VEGFR fully humanised mAb	$758m	$1,855m
9	Xalkori	Crizotinib	Pfizer	ALK kinase inhibitor	$594m	$2,486m
10	Iressa	Gefitinib	AstraZeneca	EGFR kinase inhibitor	$528m	$6,406m
11	Tecentriq	Atezolizumab	Roche	PD-L1 targeted mAb	$495m	$654m
12	Alecensa	Alectinib	Roche	ALK kinase inhibitor	$368m	$620m
13	Taxotere	Docetaxel	Sanofi	Anti-mitotic	$195m	$26,465m
14	Gemzar	Gemcitabine	Eli Lilly	Nucleoside analogue	$111m	$15,385m
15	Zykadia	Ceritinib	Novartis	ALK kinase inhibitor	$87m	$288m
16	Portrazza	Nicitumumab	Eli Lilly	EGFR recombinant human mAb	$10m	$26m
	-	Methotrexate	Generic	Folate antimetabolite	Used since 1950	
	Taxol	Paclitaxel	Generic	Anti-mitotic	N/A	
	Paraplatin	Carboplatin	Generic	DNA-Alkylating agent	N/A	

Many of these drugs are approved and used for more than one indication
Source: Company reports; Hardman & Co Life Sciences Research

High incidence and poor prognosis for NSCLC demonstrate that it is a market of unmet need, with ca.450,000 people living with lung and bronchus cancer in the US. In the event that SCIB2 could be launched with a similar price to Opdivo or Keytyruda – annual cost in the range of $25,000-50,000 – a 10% market share would equate to sales of ca.$2bn.

With ca.20 approved and well-established drugs used currently in NSCLC and more than 354 open studies registered[5], SCIB2 would be entering an even more crowded market than SCIB1.

Moditope

The Moditope market opportunity is more complex to measure, as this immunotherapy has a completely different mechanism of action, targeting citrullinated proteins which are expressed in the majority of cancers. As such, this technology could be adapted to make multiple products across many hard-to-treat cancer indications.

Scancell is focusing its efforts and resources on triple negative breast cancer, advanced ovarian cancer and sarcoma. In sarcoma, Moditope would probably be eligible for Orphan Drug Designation, which would give it fast-track regulatory review.

Triple negative breast cancer

Breast cancer is the number-one cancer worldwide, with more than 3m women affected in the US, in 2013 and with a five-year survival rate of 89.7%. The reported decrease in the death rate due to breast cancer is believed to be a combination of early diagnosis through screening programmes, coupled with increased awareness and more efficacious drugs.

Breast cancer is classified in three categories:

- Hormone-receptor positive.
- HER2 positive.
- Triple negative.

Triple negative breast cancer, the primary target for Modi-1, is where breast cancer cells do not have oestrogen or progesterone receptors and only low levels of HER2 – hence the term triple negative – which occurs in 15-20% of women with breast cancer. Consequently, any drugs that target specifically hormone or HER2 receptors will not work. Treatment protocols consist of a combination of surgery, radiation and chemotherapy (mainly doxorubicin, epirubicin, docetaxel and paclitaxel). Triple negative breast cancer tends to occur more often in younger women and is characterised by rapid growth and metastases.

Advanced ovarian cancer

An advanced ovarian cancer is when the disease has reached stages II to IV:

- Stage II: the cancer has spread into the pelvis.
- Stage III: the cancer has spread outside the pelvis to other part of the abdomen and/or nearby lymph nodes.
- Stage IV: the cancer has spread beyond the abdomen to other parts of the body.

[5] www.cancer.gov

In 2015, there were ca.200k women living with ovarian cancer in the US and ca.22k new cases are diagnosed every year. Amongst these patients, ca.70% will be in the advanced stage due to late diagnosis. Although there has been a reduction in incidence over time, this has not been accompanied by a parallel reduction in deaths, leaving the five-year survival rate unchanged at 46.2%.

Treatments for advanced ovarian cancer consists of:

- A combination of chemotherapy and surgery (removal cancerous tissues).
- Targeted therapy with PARP inhibitor for certain patients with BRCA1 and BRCA2 mutations.

Sarcoma

Sarcomas arise from transformed cells of mesenchymal origin. As sarcomas are relatively rare, this group of cancers has not benefitted significantly from research advances compared to other cancer types, even though the five-year survival rate for advanced disease is only 16%[6]. There remains a desperate need for new active therapies for sarcomas, as evidenced by the accelerated approval of olaratumab (lartruvo) with doxorubicin in 2016 in the US for patients with soft tissue sarcomas, despite serious side effects and limited clinical data.

The types of treatment used for sarcoma include:

- **Surgery** – limb-salvage surgery or amputation.
- **Chemotherapy** – usually, a combination of two or more drugs.
- **Radiation therapy**.

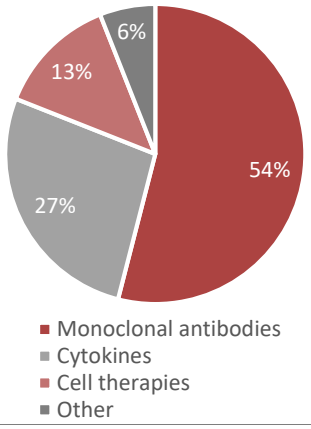
Oncology market

Global oncology drug market worth $121bn in 2017…

…giving 10-year CAGR of 7.9%

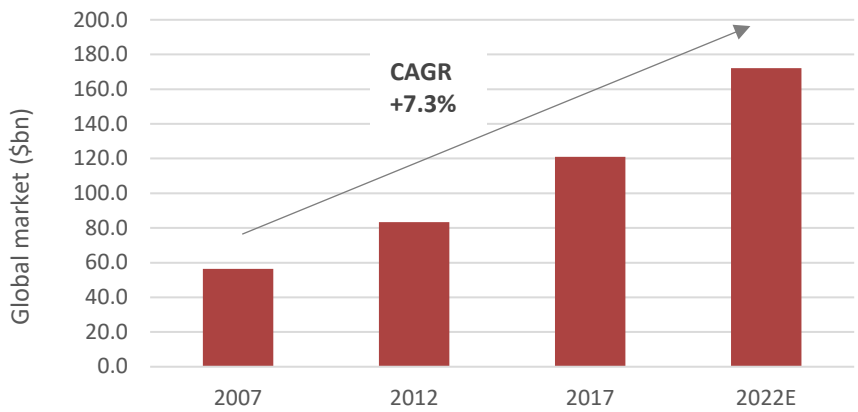
Hardman & Co estimates that the global oncology market was worth ca.$121bn in 2017 and represented 9.2% growth over 2016 in US$ terms. Our analysis is based on the ex-factory sales for the leading 110 branded drugs on the market, to which a figure representing the plethora of small/old/generic cancer drugs has been added. Our data indicates that the global oncology market has seen 7.9% CAGR over the last 10 years.

Immunotherapy programmes by technology in 2015



Source: Chang et al; Hardman & Co Life Sciences Research

Global oncology market



Source: Hardman & Co Life Sciences Research

[6] American Cancer Society 2016.

Cancer drugs derived from antibodies represented 25% of the market in 2016

Over the last decade, the global oncology market has been driven by sales of drugs derived from antibodies[7], which represented an estimated 25% of the market in 2016, at $30.1bn. Given the enormity of current development programmes for targeted immunotherapies, this status is unlikely to change in the next decade. This suggests that the historical growth rate of 7-8% compound will be maintained, such that Hardman & Co is forecasting the oncology market will grow to $165-175bn in 2022.

Scancell opportunity

Both of the Scancell immuno-therapy platforms have the potential to reach sales >$1bn

Given that Scancell is developing two platform technologies that are sufficiently flexible and relatively easy to produce, and can be applied to many different cancers, its products will become part of the overall immunotherapy segment of the market, which is clearly a multi-billion dollar opportunity.

Competitive landscape

Despite the success, the demand for even more efficacious drugs is enormous

It is abundantly clear that an enormous number of companies, large and small, are researching new immunotherapies, which is currently one of the hottest fields in drug development. Much of this is being driven by the success of antibody-derived therapies for cancer treatment, which recorded sales of just over $28.0bn in 2015. However, despite this obvious success, much more needs to be done. Even though many of these newer drugs are highly targeted, for a number of reasons they are proving less efficacious than had first been envisaged.

New technologies offer new approaches to overcome some of the problems observed clinically. In our opinion, the technologies fall into two categories:

- ***In-vivo*** – where the therapeutic is injected directly into the patient (and directly into the tumour in some cases).
- **Autologous** – (personalised approach) where patient's cells are removed, activated and then re-infused.

Both of Scancell's platform technologies are using the direct *in vivo* approach, with an opportunity to move into the autologous approach via the collaboration with BioNTech to evaluate Moditope-specific TCR therapy.

ImmunoBody is the only platform with a dual mechanism of action

There are several companies developing technologies that use a direct presentation *in vivo* approach. However, Scancell's ImmunoBody platform is the only approach that, in addition, has the facility for cross presentation, and it is this dual approach that generates potent higher-avidity T-cell responses needed to fight cancer effectively.

CureVac uses similar approach…

…but based on RNA

In terms of technology, CureVac has a similar approach to Scancell, with a direct presentation of the antigen, but based on an RNA vaccine instead of being DNA-based. Inovio Pharma and Oncosec are considered also to be direct competitors of Scancell. However, in our opinion, these companies have developed proprietary electroporation administration techniques and have then searched for a suitable therapeutic vaccine with which they could use this method of administration. In contrast, Scancell has the proprietary and clever cancer immunotherapy platforms and can use any suitable electroporation or other delivery method to administer the drug, i.e. it can simply buy in the appropriate technology to overcome a problem – that of drug administration.

[7] Chang, S. Global R&D is advancing the cancer immunotherapy field. 2015

Scancell's Moditope approach, also primarily an *in vivo* approach, relies on direct administration of citrullinated peptides. The discovery that covalently linking these peptides to a TLR-based adjuvant reduces the amount of product required to induce highly effectively anti-tumour responses is a significant step forward in producing a clinically suitable formulation. Scancell is currently the only company we are aware of using citrullinated peptides as potential cancer vaccines and it has a strong patent position in this area.

The majority of companies are using an autologous approach, which, in our opinion, is much more complex and expensive to perform.

Cancer immunotherapy development companies

Company	Approach	Technology
In vivo	**Direct or cross presentation**	
Advaxis	Attenuated *listeria* delivered bioengineered plasmids	*Lm*
Amgen	Engineered attenuated herpes simplex virus	T-VEC
Bavarian Nordic	Live virus vaccine platform	
BioNTech	Personalised mRNA vaccines	IVAC
CureVac	Viral-RNA vaccines	RNActive
Inovio Pharma	Viral DNA vaccine + Electroporation	SynCon
Oncosec Medical	Electroporation + DNA (IL-12) vaccine	ImmunoPulse
PsiOxus	'Armed' DNA vaccine	EnAd
Western Oncolytics	Viral derived technology delivering multiple immunotherapies in a single construct	WO-12
In vivo	**Direct and cross presentation**	
Scancell	**DNA immunotherapy + electroporation (bought in)**	**ImmunoBody**
In vivo	**Citrullinated epitopes**	
Scancell	**Peptide immunotherapy**	**Moditope**
Autologous	**Personalised approach**	
Adaptimmune	Autologous TCR vaccine	-
Asterias BioTher.	Autologous dendritic cell vaccine	AST-VAC1
Bluebird Bio	Autologous CAR-T-cell therapy	-
Cellectis	Autologous CAR-T-cell vaccine	TALEN
Dendreaon	Autologous dendritic cell vaccine	Provenge
Immunocore	Autologous CAR/TCR stimulation	ImmTAC
Juno Therapeutics	Autologous CAR-T-cell vaccine	-
Kite Pharma	Autologous CAR vaccine	eACT
NorthWest BioTher.	Autologous dendritic cell vaccine	DCVax
OSE Immunother.	Autologous CAR-T-cell vaccine	T-cellerator Memopi PENTRA

CAR = Chimeric antigen receptor; TCR = T-cell receptor; TAM = Tumour associated macrophages
This list is not comprehensive
Source: Hardman & Co Life Sciences Research

The autologous approach is time-consuming and very expensive

It should be noted that, although we have endeavoured to be as thorough as possible in identifying the most relevant immuno-oncology companies working in the field that might compete with Scancell's technology, our list should not be considered comprehensive.

Financial analysis

Profit & Loss

In the medium term, the P&L account will be driven largely by two numbers, the corporate overhead/administration costs (SG&A) and the investment in R&D programmes and clinical trials.

- **R&D:** Overall forecasts have been reduced for fiscal 2018 and 2019 to reflect the movement of SCIB2 clinical trial costs (ca.£5m) from Scancell to CRUK. However, countering this will be the commencement of the SCIB1 trial in 4Q'18 and Modi-1, which is scheduled to start in 1H'19.
- **SG&A:** A slight movement in senior personnel is expected to have a modest impact on the corporate overhead. Therefore, our forecasts have been increased by £0.1m to -£2.0m for fiscal 2018; and rising 5% p.a. thereafter.
- **R&D tax credits:** These are calculated at 20% (conservative) of R&D spend. Actual payment of the cash by HMRC is assumed to be received in the following financial year.

P&L						
Year-end April (£m)	**2015**	**2016**	**2017**	**2018E**	**2019E**	**2020E**
Sales	0.00	0.00	0.00	0.00	0.00	0.00
SG&A	-0.75	-0.75	-1.00	-1.73	-2.00	-2.10
R&D	-2.12	-2.12	-2.01	-2.77	-3.50	-5.90
EBITDA	-2.84	-2.84	-2.99	-4.46	-5.47	-7.97
Depreciation and amortis.	-0.03	-0.03	-0.02	-0.03	-0.03	-0.03
Licensing/Royalties	0.00	0.00	0.00	0.00	0.00	0.00
Underlying EBIT	**-2.87**	**-2.87**	**-3.01**	**-4.50**	**-5.50**	**-8.00**
Share-based costs	-0.09	-0.09	-0.04	-0.05	-0.06	-0.07
Exceptional items	0.00	0.00	0.00	0.00	0.00	0.00
Statutory EBIT	-2.96	-2.96	-3.04	-4.55	-5.56	-8.07
Net financial income	0.13	0.13	0.01	0.05	0.04	0.05
Underlying pre-tax profit	**-2.74**	**-2.74**	**-2.99**	**-4.44**	**-5.46**	**-7.95**
Reported pre-tax profit	-2.83	-2.83	-3.03	-4.50	-5.52	-8.02
Reported taxation	0.41	0.41	0.45	0.95	0.70	1.18
Tax rate	-15%	-15%	-15%	-21%	-13%	-15%
Underlying net income	**-2.32**	**-2.32**	**-2.55**	**-3.49**	**-4.76**	**-6.77**
Statutory net income	-2.41	-2.41	-2.58	-3.54	-4.82	-6.84
Ordinary 0.1p shares:						
Period-end shares (m)	225.0	225.0	227.6	261.6	395.4	395.4
Weighted average (m)	225.0	225.0	227.6	261.6	318.0	395.4
Fully diluted shares (m)	240.5	240.5	249.2	254.8	289.0	356.7
Underlying basic EPS (p)	**-1.03**	**-1.03**	**-1.12**	**-1.34**	**-1.50**	**-1.71**
Statutory basic EPS (p)	-1.07	-1.07	-1.14	-1.36	-1.51	-1.73
U/l fully-diluted EPS (p)	**-0.93**	**-0.93**	**-1.00**	**-1.21**	**-1.33**	**-1.56**
Fully-diluted EPS (p)	-0.97	-0.97	-1.01	-1.23	-1.35	-1.57
DPS (p)	0.00	0.00	0.00	0.00	0.00	0.00

Source: Hardman & Co Life Sciences Research

Balance sheet

- **Net cash:** At 31st October 2017, Scancell had net cash of £5.0m which is being used to prepare the groundwork for its upcoming clinical trial programme, and for general corporate purposes.
- **Capital increases:** Scancell raised £4.73m (net) through the issue of new Ordinary shares at 10p per share in May 2017. In order to fund the proposed Phase II SCIB1 combination trial and to initiate Modi-1 trials, our forecasts assume that the company will raise a further £10m (gross) within the next six months.
- **Value inflection points:** More cash will be required in the future, but headline data from some of the clinical trials should be available by then, with positive outcomes representing significant value inflection points.

Balance sheet						
@30th April (£m)	**2015**	**2016**	**2017**	**2018E**	**2019E**	**2020E**
Shareholders' funds	6.75	9.99	6.50	15.81	8.97	0.49
Cumulated goodwill	0.00	0.00	0.00	0.00	0.00	0.00
Total equity	6.75	9.99	6.50	15.81	8.97	0.49
Share capital	0.22	0.26	0.26	0.26	0.26	0.26
Reserves	6.53	9.73	6.24	15.55	8.71	0.23
Long-term loans	0.00	0.00	0.00	0.00	0.00	0.00
Short-term debt	0.00	0.00	0.00	0.00	0.00	0.00
less: Cash	3.06	6.53	2.67	12.31	5.07	-3.70
less: Marketable secs.	0.00	0.00	0.00	0.00	0.00	0.00
Invested capital	**3.70**	**3.46**	**3.83**	**3.50**	**3.90**	**4.19**
Fixed assets	0.09	0.06	0.09	0.06	0.06	0.06
Intangible assets	0.00	0.00	0.00	0.00	0.00	0.00
Inventories	0.00	0.00	0.00	0.00	0.00	0.00
Trade debtors	*0.00*	*0.00*	*0.00*	*0.00*	*0.00*	*0.00*
Other debtors	*0.14*	*0.12*	*0.10*	*0.10*	*0.10*	*0.10*
Tax credit/(liability)	*0.66*	*0.44*	*0.75*	*0.70*	*1.18*	*1.56*
Trade creditors	*-0.37*	*-0.32*	*-0.27*	*-0.32*	*-0.37*	*-0.37*
Other creditors	*-0.23*	*-0.26*	*-0.26*	*-0.45*	*-0.49*	*-0.57*
Debtors less creditors	0.19	-0.01	0.32	0.02	0.42	0.71
Invested capital	**3.70**	**3.46**	**3.83**	**3.50**	**3.90**	**4.19**
Net cash/(debt)	**3.06**	**6.53**	**2.67**	**12.31**	**5.07**	**-3.70**

Source: Hardman & Co Life Sciences Research

Cashflow

- **Change in net cash**: Cashflow is dictated by the investment in R&D and SG&A, offset by R&D tax credits, flowing through from the P&L account.
- **Tax credits:** There is usually a timing difference between R&D investment and the cash rebate receivable from HMRC.
- **Cap-ex:** Given that manufacturing activities are all out-sourced, the company has minimal capital expenditure requirements.
- **Capital increase:** As stated above, we have incorporated a capital increase of £10m (gross) into our forecasts for fiscal 2018.

Cashflow statement						
Year-end April (£m)	**2015**	**2016**	**2017**	**2018E**	**2019E**	**2020E**
Underlying EBIT	-2.87	-3.01	-4.50	-5.50	-8.00	-10.00
Depreciation	0.03	0.02	0.03	0.03	0.03	0.03
Amortisation	0.00	0.00	0.00	0.00	0.00	0.00
Inventories	0.00	0.00	0.00	0.00	0.00	0.00
Working capital	0.08	-0.01	-0.02	-0.02	-0.02	-0.02
Other	0.00	0.00	0.00	0.00	0.00	0.00
Company op cashflow	**-2.76**	**-3.00**	**-4.49**	**-5.49**	**-7.99**	**-9.98**
Net interest	0.02	0.00	0.01	0.04	0.05	0.03
Tax	0.12	0.67	0.64	0.95	0.70	1.18
Free cashflow	**-2.62**	**-2.33**	**-3.84**	**-4.49**	**-7.23**	**-8.77**
Dividends	0.00	0.00	0.00	0.00	0.00	0.00
Acquisitions	0.00	0.00	-0.06	0.00	0.00	0.00
Disposals	0.00	0.00	0.00	0.00	0.00	0.00
Cashflow after invests.	**-2.51**	**-2.32**	**-3.86**	**-4.49**	**-7.23**	**-8.77**
Capital increase	0.00	5.79	0.00	14.13	0.00	0.00
Change in net debt	**-2.51**	**3.47**	**-3.86**	**9.64**	**-7.23**	**-8.77**
Hardman FCF/share (p)	-1.2	-1.0	-1.5	-1.4	-1.8	-2.2
Opening net cash	5.57	3.06	6.53	2.67	12.31	5.07
Closing net cash	**3.06**	**6.53**	**2.67**	**12.31**	**5.07**	**-3.70**

Source: Hardman & Co Life Sciences Research

Valuation

Discounted cashflow

DCF is not an appropriate valuation methodology at this stage

The best approach to valuing biopharmaceutical companies is to prepare detailed discounted cashflow analyses of key products through to patent expiry, and then to risk-adjust the NPV based upon industry standards for the probability of the product reaching the market. However, in the case of Scancell, the assets are considered to be at too early a stage with no stated commercial strategy – assets will probably be licensed out to big pharma for commercialisation – to undertake a reliable DCF valuation, without exhaustive analysis of the market opportunities, penetration rates, and potential milestones and royalty payments.

Scancell's proprietary technologies are targeting a 'hot' field…

Suffice to say, Scancell's proprietary technologies are in a therapeutic area of significant unmet medical need, which is also considered to be 'hot'. Products that have achieved a successful regulatory outcome and been commercialised have all seen rapid uptake and generated >$1bn sales, which suggests that these flexible assets will be very attractive to big pharma and/or biotech companies. To that extent, it is probably more relevant to look at what large pharma is prepared to pay to gain access to such technologies.

Comparative valuation – M&A

…that is attracting the major players…

…who are willing to pay handsome prices for the right assets

Another way of determining valuation looks at the prices that acquirers have been prepared to pay for the novel technology and assets. What is noticeable in the table below is the ca.$1,000m deal that Bavarian Nordic signed with BMS in March 2015 for the rights to license and commercialise PROSTVAC, which is in Phase III development for the treatment of asymptomatic or minimally symptomatic metastatic castration-resistant prostate cancer. In October 2017, the partnership between Eli Lilly and CureVac was announced, which could generate up to $1.8bn for the development and commercialisation of up to five cancer vaccines based on RNActive technology to deliver mRNA across multiple tumour types.

On the acquisition side, the proposed buy-out of Juno by Celgene and Kite by Gilead for $9bn and $12bn, respectively, show the huge price tags that big organisations are willing to pay to gain access to interesting technology platforms in cancer immunotherapy; and we note that Scancell has two distinct platforms.

Deal comparators – cancer vaccine assets

Licensor	Licensee	Type of deal	Stage of development	Date	Upfront ($m)	Milestones ($m)	Milestones
Celgene	Juno Therapeutics	Acquisition	Phase III	Jan-18	9,000		Under discussion
AbbVie	Turnstone Biologics	Global collaboration	Phase I/II	Oct-17	-	-	Exclusive option to license up to three Turnstone oncolytic viral immunotherapies
Eli Lilly	CureVac	Collaboration	Phase I	Oct-17	50 +53	1,700	$50m upfront + $53m equity investment +$1.7m in milestones
Gilead	Kite Pharma	Acquisition	Phase II	Aug-17	11,889		
Genentech	Inovio	Collaboration	Phase I/II	Jun-17	-	-	Evaluation of Tecentriq in combination with INO-5401 and INO-9012
Amgen	Immatics	Collaboration	Phase I/II	Jan-17	30	500	$500m in development, regulatory and commercial milestones for each programme + double-digit royalties
Roche	BioNTech	Global collaboration	Pre-clinical	Sept-16	310	Undisclosed	Upfront includes some near-term milestones co-development and profit sharing elements
Merck & Co	Moderna Therapeutics	Collaboration	Pre-clinical	Jun-16	200	Undisclosed	Undisclosed, plus royalties
AstraZeneca	Moderna Therapeutics	Collaboration	Pre-clinical	Jan-16+ Aug-16	-		Co-development agreement for selected oncology targets + $140m investment in Moderna
Agenus	PhosImmune	Acquisition	Pre-clinical	Dec-15	9.9	35	$35m on achievement of certain milestones
AstraZeneca	Inovio	Licence	Phase I/II	Aug-15	27.5	700	$700m (development and commercial milestones, plus double-digit royalties)
Bristol-Myers Squibb	Bavarian Nordic	Licence	Phase III	Mar-15	60	915	$915m ($80m if exercised, $110m for regulatory, $230m development milestones, up to $495m in sales and double-digit royalties
Boehringer Ingelheim	CureVac	Licence	Pre-clinical	Sep-14	45	550	$550m (for sales plus royalties)
Roche	Immatic	Collaboration	Pre-clinical	Nov-13	17	Undisclosed	Undisclosed, plus royalties
Bayer	Compugen	Licence	Pre-clinical	Aug-13	10	530	$530m ($30m preclinical activities, $500m potential milestone payment and high single-digit royalties)

Source: Hardman & Co Life Sciences Research

Historically, an analysis of a large number of early-stage deals, shows that companies have been willing to pay $10m to $45m for pre-clinical assets followed by big milestone payments if successful, with high single-digit to double-digit royalties.

Cancer vaccine research, with the use of CPIs, is a hot area of development. Several companies have clinical development pipelines using more complex techniques, compared with the flexibility of Scancell's platforms.

Roche pays BioNTech an upfront of $310m to gain access to novel mRNA vaccine platform

Roche, through its wholly-owned subsidiary Genentech, announced a global collaboration deal with BioNTech, whereby Genentech's immunotherapy portfolio would be combined with BioNTech's proprietary messenger RNA cancer vaccine platform to create tailored (personalised) immunotherapies for a number of cancer types. The upfront payment, including some clearly achievable, near-term royalties was stated to be $310m. Both companies will share the development costs, along with a longer-term profit-sharing arrangement. This deal again highlights the high prices that major pharmaceutical companies are willing to pay to gain access to new technologies.

AZN recently increased its stake in Moderna

AstraZeneca (AZN) originally agreed a collaboration with Moderna Therapeutics in 2013 to discover, develop and commercialise mRNA therapeutics for the treatment of cardiovascular, metabolic and renal diseases, and some selected targets in oncology. This collaboration was extended in January 2016 through a new collaborative agreement for two specific pre-clinical immune-oncology programmes. Details of the financial terms were not disclosed. However, in August 2016, AZN did participate in a preferred stock placing undertaken by Moderna, investing $140m which equated to a 9% holding in the fully-diluted share capital.

MRK also signed a collaboration deal with Moderna…

…for mRNA cancer vaccine…

…with a $200m upfront payment

In June 2016, Moderna also agreed a collaboration agreement with Merck & Co (MRK) for a pre-clinical stage mRNA vaccine, which included a $200m upfront. Both companies will share the development costs for an mRNA-based personalised cancer vaccine which is expected to start clinical trials next year. MRK has the option, after human proof-of-concept data, to make an additional undisclosed payment to Moderna. Upon that exercise, the pair will split costs and profits equally under a worldwide collaboration arrangement, with Moderna retaining the right to co-promote the vaccines in the US. The mRNA vaccine technology encodes a patient's specific neoantigens – unique mutations present in a specific tumour – and is intended to elicit a specific immune response to destroy those cancer cells. The programme will focus on several types of cancer and the vaccines are expected to be synergistic with CPIs, such as Keytruda, MRK's anti-PD-1.

Comparative valuation – peer analysis

The EV of Scancell does not reflect properly either the achievement or the IP position…

Scancell is trading on an enterprise value of ca.£34m compared to a cumulative investment of £29m to get the company to where it is today. Whether this is a true reflection of valuation is difficult to say.

…compared with the EV of Inovio is which is 4.9x greater…

…and with its main asset being only the administration technology

Inovio has a diverse pipeline, with several vaccines in development, for HIV, Hepatitis B and C, and universal influenza, but only one of these is currently in clinical development (Phase II). Inovio has developed its own DNA plasmid cancer immunotherapy (SynCon), on which there is little clinical data available. The vaccine is administered via Inovio's own proprietary electroporation administration technology, for which it has managed also to sign a number of licensing deals. In contrast, Scancell has developed two proprietary immunotherapy platforms and has the freedom to choose which electroporation technology or alternative delivery methodology to use to administer its products. In our opinion there is much greater value in the immunotherapy platform than in the delivery technology. Despite this, Inovio trades on an EV 4.9x greater than that for Scancell.

The following table shows the comparative data for a group of relevant quoted peer companies. It is clear from the table that the markets put far greater value on companies that have validated technology, as evidenced by the signing of licensing deals. Looking at this data in its entirety suggests that there is considerable upside potential for Scancell.

Peer group valuations

Company	Advaxis ADXS	Bavarian Nordic BAVA	Inovio INO	OncoSec ONCS	OSE Immuno OSE	Scancell SCLP
Local currency	$	NKR	$	$	€	£
Share price	2.7	244.0	4.1	1.96	3.5	12.5
Shares in issue (m)	41.1	32.0	90.3	35.5	14.4	312.1
Market cap. (lc)	111.7	7,803.4	372.0	69.6	49.6	39.0
Market cap. (£m)	80.4	711.3	267.7	50.1	44.3	39.0
Cash	15.0	2,808.0	141.9	14.7	20.5	5.0
Debt	0.0	0.0	0.0	1.1	0.0	0.0
EV (lc)	96.6	4,995.4	230.1	53.8	29.1	34.0
EV (£m)	**69.5**	**455.4**	**165.6**	**38.7**	**26.0**	**34.0**
Relative EV	2.0x	13.4x	4.9x	1.1x	0.8x	-
I-O stage of development	Phases I/II/III	Phases I/II/III	Phases I/II	Phase II	Phase I/II/III	Phases I/II
Licensing deals	3	3	9	0	4	2

Prices taken at close of business on 14th February 2018
lc = local currency
Source: Hardman & Co Life Sciences Research

Company matters

Registration

Scancell Holdings is incorporated in the UK with company registration number: 06564638

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Board of Directors

Board of Directors				
Position	**Name**	**Nominations**	**Remuneration**	**Audit**
Chairman	Dr John Chiplin			
Chief Executive Officer	Dr Cliff Holloway			
Chief Scientific Officer	Prof Lindy Durrant			
Development Director	Dr Sally Adams			
Non-executive director	Kate Cornish-Bowden		C	M
Non-executive director	Dr Matthew Frohn		M	C
Non-executive director	Dr Richard Goodfellow			
Non-executive director	Dr Alan Lewis			

M = member; C = chair
Source: Company reports

Dr John Chiplin – Chairman

John is based in San Diego and provides significant international experience in the US life science and technology industries. Recently, John was instrumental in the NASDAQ IPOffering of Benitec Biopharma (ASX: BLT; NASDAQ BNTC), a clinical stage biotechnology company, where he has been an NED since 2010. He also serves on the boards of Cynata Therapeutics, Adalta, Batu Biologics, Prophecy, ScienceMedia and the Coma Research Institute. Previously, John was President and CEO of Polynoma, a Phase III cancer vaccine company, and from 2006-09 he was CEO of Arana Therapeutics. Prior to this, he was head of the UK ITI Life Sciences investment fund, managing negotiations regarding funding with Government Ministers.

Cliff Holloway – Chief Executive Officer

Cliff was appointed in January 2018 and brings over 25 years of life science industry experience to Scancell in the development and commercialisation of emerging technologies and therapeutic products, including licensing, M&A, corporate finance and operations management. Most recently, he was Chief Business and Operating Officer of Benitec Biopharma Ltd. Prior to this, he was Managing Director of Sienna Cancer Diagnostics Ltd (ASX:SDX), and also for therapeutic antibody development companies Immune System Therapeutics Ltd and Biosceptre International Ltd. He was formerly VP of Business Development at Arana Therapeutics Ltd, which was acquired by US-based Cephalon Inc (now Teva) in 2009, and he is currently a director of investment fund Newstar Ventures Pty Ltd. Cliff holds a Bachelor of Pharmacy and a PhD in Medicinal Chemistry from the University of Nottingham.

Professor Lindy Durrant – Chief Scientific Officer.

Professor Lindy Durrant is an internationally recognised immunologist in the field of tumour therapy. She has worked for over 20 years in translational research, developing products for clinical trials, including monoclonal antibodies for diagnostic imaging and therapy and cancer vaccines. She has a personal Chair in Cancer Immunotherapy at the Department of Clinical Oncology at the University of Nottingham.

Dr Sally Adams – Development Director

Sally was Head of Neurology & Virology at British Biotech and Development Director at Neures Limited before becoming an independent consultant providing drug development and management services in the biotechnology and pharmaceutical sectors, specialising in biological entities. She has worked on many complex projects over the past 25 years, including anti-infective vaccines, cancer immunotherapies and an innovative stem cell treatment for visual dysfunction. Sally previously worked as a development consultant to Scancell, providing guidance on the development of SCIB1, before her appointment as Development Director in May 2014.

Kate Cornish-Bowden – Non-Executive Director

Kate is a Chartered Financial Analyst and holds a Masters in Business Administration. She was an executive director and senior portfolio manager at Morgan Stanley IM's Global Core Equity Team prior to becoming its managing director. Kate has acted as a consultant providing research to private equity and financial training firms. She was appointed a director of Investec Structured Products Calculus VCT plc in February 2011.

Dr Matthew Frohn – Non-Executive Director

Matthew started his career as a clinical and research scientist before moving into venture capital in 1999. He originally joined Oxford Technology, making seed investments into start-up and early-stage technology companies, predominantly in healthcare. He co-founded Longwall Venture Partners, a £70m early-stage technology investment company. Matthew has a DPhil in Biochemistry from the University of Oxford.

Dr Richard Goodfellow – Non-Executive Director

Along with Professor Durrant, Richard was a co-founder and former CEO of Scancell. Together, they were responsible for developing the company to where it is today. Richard has over 25 years' experience in the pharmaceutical industry, in both multinational drug companies and smaller entrepreneurial biopharma companies. He stepped down as CEO in January 2018, but remains on the Board as an NED.

Dr Alan Lewis – Non-Executive Director

Alan has a proven track record in the US life sciences industry and is currently President and CEO of DiaVacs, a San Diego-based clinical-stage biotechnology company. He has held senior positions at several life science companies, including Celgene, Ambit Biosciences, Medistem, Novocell and Signal Therapeutics. He is also on the Board of Directors of NASDAQ-listed companies Biomarin and Assembly Biosciences.

Senior Management

Keith Green – Financial Director

Keith is a chartered accountant who spent 20 years in the accounting profession before joining a private medical diagnostic company as Finance Director. Since 2003, he has taken on many consultancy and interim finance roles for private and AIM-listed companies in the life science sector. Keith started working for Scancell on a part-time basis in January 2010 and took up this full-time role in September 2016.

Capital increases

Since its listing on PLUS in 2008, Scancell has raised just under £24m of capital. The cash balance at the end of October 2017 was £5.0m, which will be sufficient to undertake the planning stages for the proposed clinical trial programme. Further capital, estimated at £10m (gross) will be required to fund the clinical trial programmes described earlier in this document.

Comparative valuation

Comment	Date	Shares (m)	Price (p)	Raised (£m)	Shares o/s (m)	Valuation (£m)
Prior to flotation on PLUS				4.68	76.0	
Flotation on PLUS; Placing at 6.0p	Sep-08	26.0	6.0	1.56	102.0	6.12
Placing @ 6.0p	Dec-08	0.7	6.0	0.04	102.8	6.17
Open offer at 4.5p per share	Mar-10	51.4	4.5	2.31	154.1	6.94
Placing at 4.5p per share	Apr-10	4.6	4.5	0.21	158.7	7.14
Placing @ 4.5p	May-10	0.5	4.5	0.02	159.3	7.17
Issue new ordinary shares @ 9.55p	Jan-11	0.3	9.6	0.02	159.5	15.23
Subdivision of 1p shares into new 0.1p shares	Jun-11	0.0	0.0	0.00	159.5	15.23
Placing @ 5.0p	Jun-11	34.6	5.0	1.73	194.1	9.70
Issued to Scancell Ltd shareholders	Jul-13	20.0	22.5	0.00	214.1	48.12
Open offer @ 22.5p (1-for-22)	Jul-13	8.9	22.5	2.00	223.4	50.26
Exercise of option (Ichor)	Nov-13	1.6	4.5	0.07	225.0	0.00
Placing @ 17p	Mar-16	20.0	17.0	3.40	245.0	41.61
Open offer @ 17p (1-for-10)	Apr-16	16.6	17.0	2.82	261.6	44.46
Placing @ 10p	May-17	50.5	10.0	5.0	312.1	31.21
	Total			**23.9**		

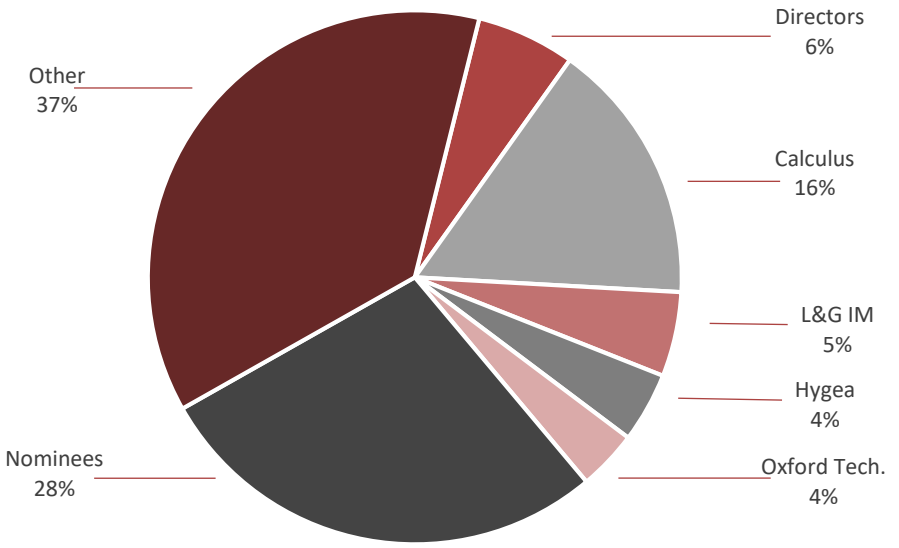
Prior to June 2011, the number of shares and share prices have been corrected for the 100-for-1 subdivision

Source: Hardman & Co Life Sciences Research

Share capital

The company has 312,058,098 Ordinary shares of 0.1p nominal value in issue. There are 37.8 million options outstanding, or 10.8% of the fully-diluted share capital.

Major shareholders



Source: Company reports

Risks

Background

Investments in small, early-stage pharmaceutical companies carry a significant risk and investors must be aware of this fact. In our opinion, the following risks are particularly relevant. Each of them could have an impact on time to reach market, cash flow breakeven and profitability.

Financial/dilution risk

The company has sufficient cash to fund the preparative work needed for its clinical development programme. However, it will require £10m of new capital in order to undertake the planned trials. There is no guarantee that the company will be successful in raising such funds, nor on the terms that such capital is raised, which could be dilutive to shareholders.

Commercialisation

Management has not stated its plans for commercialisation. For large-scale clinical trials and commercialisation of its assets the company is likely to seek a partner through an out-licensing arrangement. There is no guarantee that this would be on terms that would be beneficial to shareholders.

Patent robustness

As with all IP-rich companies, there is a risk that the intellectual property is insufficiently covered by the global patents, allowing a competitor to gain market access. Any litigation could involve significant costs and uncertainties.

Regulatory

It is important for companies to liaise with regulators on a regular basis throughout the development programme. Any inadequacies could lead to regulatory action, such as cessation of product development and loss of manufacturing or product licences.

Share liquidity

As with many small-cap companies listed on AIM, there can be difficulty in buying and selling shares in volume. Market-makers only guarantee prices in a very small number of shares.

Competition

The company operates in a market dominated by larger multinational competitors, most of which have significant financial resources to fund development programmes, marketing activities, etc.

Appendix

Electroporation (EP)

When high-amplitude, short-duration pulsed electric fields are applied to cells and tissues, the permeability of the cell membranes and tissue is increased. This increase in permeability has been explained by the temporary appearance of aqueous pores within the cell membrane, a phenomenon termed electroporation. The DNA or gene of a protein drug can be injected through these pores and, once within the cell, the DNA will be decoded, and the cell will make the drug.

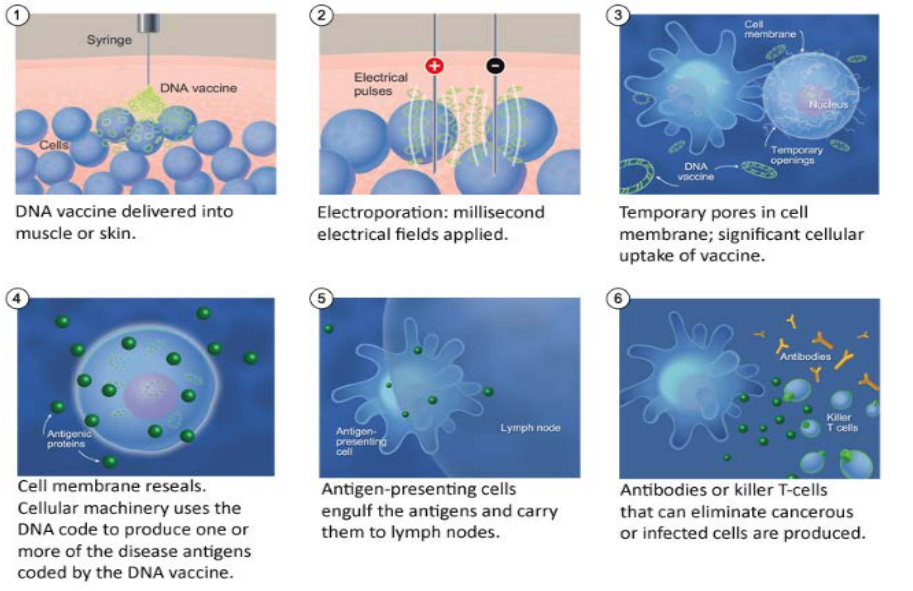
EP has been demonstrated to increase the cellular uptake of DNA plasmids by at least 1,000-fold compared with the delivery of 'naked DNA' alone, which means that much smaller doses of DNA are required to get good uptake and for a clinically relevant dose of drug to be made in the cells. The drug may then act within the cell or be ejected to have a wider effect in the local environment or across the whole body.

Scancell's ImmunoBody therapies are delivered into muscle cells using the patented new-generation TriGrid 2.0 electroporation delivery system from Ichor Medical.

Electroporation delivery

Source: Ichor Medical Systems

Electroporation delivery



Source: Inovio Pharmaceuticals Inc

Advantages

- **Versatility:** effective with nearly all cell and species types.
- **Efficiency:** a high percentage (>80%) of cells are transfected with the target DNA/protein/gene without jeopardising the viability of the cell.
- **Small scale:** uses much lower amounts of material.

Disadvantages

- **Cell damage:** if electric pulses are the wrong length or too intense, cell membrane pores may not close, causing cells to rupture.
- **Non-specific:** any material can enter cell at the time of electro-permeability, making it non-specific, which could lead to improper cell function and cell death.

Glossary

Antigen	An antigen is a substance that has the potential to cause the body to mount an immune response against it. It helps the immune system to determine whether something is self or non-self (foreign). Non-self antigens are recognised by the immune system as a threat and will trigger the immune response.
Autophagy	Autophagy is a normal physiological process that deals with destruction of cells in the body. It maintains homeostasis or normal functioning by protein degradation and turnover of the destroyed cell organelles for new cell formation. During cellular stress, when there is deprivation of nutrients and/or growth factors, the process of autophagy is increased. Thus, it may provide an alternate source of intracellular building blocks/substrates that may generate energy to enable continuous cell survival.
Avidity	Avidity is a measure of the potency of T-cells characterised by the immune cell's ability to recognise low amounts of antigen processed and presented on the tumour cell surface by MHC molecules. High-avidity T-cells are able to recognise tumour cells with only a few copies of antigen whereas low-avidity T-cells require higher levels of antigen expression to be present.
CAR-T	Chimeric antigen receptors (CAR) are engineered receptors which graft an arbitrary specificity onto an immune effector cell (T-cell). Typically, these receptors are used to graft the specificity of a monoclonal antibody onto a T-cell, with transfer of their coding sequence facilitated by retroviral vectors.
Checkpoint inhibitor	Checkpoint inhibitors (usually monoclonal antibodies) block the activity of certain normal proteins on cancer cells, or the proteins on T-cells that respond to them. The result is to remove the blockade that prevented T-cells from recognising the cells as cancerous and can therefore facilitate the immune recognition of the tumour cells.
Citrullination	The conversion of arginine to citrulline by peptidylarginine deiminase enzymes in the presence of high levels of Ca^{2+}. Citrullination yields only a small change in molecular mass (less than one Dalton) and the loss of a positive charge, yet this process can have considerable consequence on protein structure and protein-protein interactions. In addition, citrulline is not one of the twenty standard amino acids incorporated into normal proteins; therefore, when peptides containing citrulline are presented to the immune system by MHC class II molecules they appear as non-self.
Epitope	This is the part of an antigen that is recognised by the immune system.
Major histocompatibility complex	MHC is a set of cell surface proteins essential for the immune system to recognise foreign molecules. The main function of MHC molecules is to bind to peptide antigens and display them on the cell surface for recognition by the appropriate T-cells. The MHC gene family is divided into three subgroups: class I, class II, and class III. Class I MHC molecules can only be recognised by CD8 co-receptors. Class II MHC molecules are recognised only by CD4 co-receptors.
Neo-epitope	Neo-epitopes function as unique tumour-specific antigens by which the adaptive immune system can selectively target cancer cells. As such, neo-epitopes are central to all forms of immunotherapy.

Plasmid	A plasmid is a small DNA molecule within a cell, which is physically separated from chromosomal DNA and can replicate independently. Plasmids are most commonly found as small circular, double-stranded DNA molecules.
T-cell receptor	A TCR molecule found on the surface of T-cells, which is responsible for recognising fragments of antigen as peptides bound to MHC molecules.
Tumour-associated antigen	A TAA is an antigen produced in much larger quantities in cancer cells than in normal cells, or an antigen that is not normally produced in the tissue in which the cancer has developed.

Abbreviations

APC	Antigen presenting cell
CAR	Chimeric antigen receptor
CDD	Centre for Drug Development
CPI	Checkpoint inhibitor
CTA	Clinical trial application
CTL	Cytotoxic T-lymphocyte
EP	Electroporation
GMP	Good manufacturing practice
HLA	Human leukocyte antigen
IFN	Interferon
IND	Investigational New Drug
IO	Immuno-oncology
MHC	Major histocompatibility complexes
NICE	National Institute for Health and Care Excellence
NSCLC	Non-small cell lung cancer
OS	Overall survival
PAD	Peptidyl arginine deaminase
RFS	Recurrence-free survival
TAA	Tumour-associated antigen
TCR	T-cell receptor
TIL	Tumour-infiltrating lymphocyte
TLR	Toll-like receptor
Tregs	Regulatory T-cells

Notes

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(Disclaimer Version 4 – Effective from January 2018)

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Some professional investors, who are subject to the new MiFID II rules from 3rd January, may be unclear about the status of Hardman research and, specifically, whether it can be accepted without a commercial arrangement. Hardman's company research is paid for by the companies about which we write and, as such, falls within the scope of 'minor non-monetary benefits', as defined in the Markets in Financial Instruments Directive II.

In particular, Article 12(3) of the Directive states: 'The following benefits shall qualify as acceptable minor non-monetary benefits only if they are' (b) 'written material from a third party that is commissioned and paid for by an[sic] corporate issuer or potential issuer to promote a new issuance by the company, or where the third party firm is contractually engaged and paid by the issuer to produce such material on an ongoing basis, provided that the relationship is clearly disclosed in the material and that the material is made available at the same time to any investment firms wishing to receive it or to the general public;'

The fact that we are commissioned to write the research is disclosed in the disclaimer, and the research is widely available.

The full detail is on page 26 of the full directive, which can be accessed here: http://ec.europa.eu/finance/docs/level-2-measures/mifid-delegated-regulation-2016-2031.pdf

In addition, it should be noted that MiFID II's main aim is to ensure transparency in the relationship between fund managers and brokers/suppliers, and eliminate what is termed 'inducement', whereby free research is provided to fund managers to encourage them to deal with the broker. Hardman is not inducing the reader of our research to trade through us, since we do not deal in any security.

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